

博士論文

Measures of research and development productivity for
the pharmaceutical industry using the two-stage data
envelopment method

(2段階データ包絡法による、製薬産業の研究開発生産性の測定)

Hirohisa Shimura

志村 裕久

Table of Contents

Abstract	12
1 Introduction	17
1.1. Research background.....	17
1.1.1. Deterioration of the R&D productivity in the pharmaceutical industry.	18
1.1.2. Industry consolidation in the pharmaceutical industry	20
1.2. Literature review	23
1.2.1. Previous literature on R&D productivity in the pharmaceutical industry	23
1.2.2. Previous literature on industry consolidation in the pharmaceutical	industry26
1.3. Purpose of the dissertation	31
1.4. Organization of the dissertation.....	32
2. Methodology/Data	35
2.1. Definition of R&D productivity in this dissertation	35
2.2. Data envelopment analysis	38
2.3. Malmquist index	43
2.4. Two-Stage DEA	45
2.5. R&D productivity map (RDP map).....	50
2.6. Data descriptions	53
2.6.1. Data description on Japanese pharmaceutical industry	54
2.6.2. Data descriptions on global pharmaceutical industry	66
2.7. Statistical procedures utilized in this dissertation.....	73
2.7.1. Statistical analysis on Japanese pharmaceutical industry	73
2.7.2. Statistical analysis on global pharmaceutical industry.....	73
2.8. Summary.....	74
3. Analysis on Japanese pharmaceutical companies between 1980 and 2006	75

3.1.	Results on R&D productivity among Japanese pharmaceutical industry.....	75
3.1.1.	Results on R&D productivity.....	75
3.1.2.	Results on relationships between R&D productivity and industry consolidation	88
3.1.3.	Results on relationships between R&D productivity and therapeutic categories.....	89
3.1.4.	Results on RDP maps	91
3.2.	Discussions on analysis on Japanese pharmaceutical analysis	96
3.2.1.	Discussions on R&D productivity.....	96
3.3.	Discussions on relationships between R&D productivity and industry consolidation.....	98
3.3.1.	Discussions on relationships between R&D productivity and therapeutic categories.....	100
3.4.	Summary.....	104
4.	Analysis of global pharmaceutical companies in 2007 and 2012.....	106
4.1.	Results on global pharmaceutical company	106
4.1.1.	Results on R&D productivity.....	106
4.1.2.	Results on relationships between R&D productivity and industry consolidations	114
4.1.3.	Results on relationships between R&D productivity and therapeutic categories.....	115
4.1.4.	Results on RDP map.....	117
4.2.	Discussions on R&D productivity among global pharmaceutical industry..	120
4.2.1.	Discussions on R&D productivity.....	120
4.2.2.	Discussions on relationships between R&D productivity and industry consolidations	124
4.2.3.	Discussions on relationships between R&D productivity and therapeutic categories.....	125

4.3. Summary.....	128
5. Discussions/Conclusion.....	129
5.1. Discussions on R&D productivity.....	129
5.2. Discussions on relationships between R&D productivity and industry consolidations	131
5.3. Discussions on relationships between the R&D productivity and therapeutic categories	134
5.4. Further research topics	138
5.5. Limitations	142
5.6. Conclusion.....	143
5.7. Acknowledgement	144
Bibliography	145
APPENDIX.....	150
Appendix 1 List of new molecular entities approved in Japan from 1980 to 2006	151
Appendix 2 List of new molecular entities used for global pharmaceutical companies in 2007.....	161
Appendix 3 List of new molecular entities used for global pharmaceutical companies in 2012.....	164

List of Figures

Figure 1.1. Historical trends of R&D spending and NMEs by region.....	19
Figure 1.2. Historical trends of NMEs by region	20
Figure 2.1. Schematic view on R&D productivity by Paul et al	36
Figure 2.2. Schematic view on R&D productivity used in this dissertation.....	38
Figure 2.3. Malmquist index Formula	44
Figure 2.4. Components of Malmquist Index formula.....	45
Figure 2.5. R&D Productivity Model.....	49
Figure 2.6. R&D Productivity Model algorithm	50
Figure 2.7. Schematic view on the RDP map	51
Figure 3.1. Accumulated R&D spending, actual, adjusted, and optimized number of NMEs for Japanese pharmaceutical companies in 1997	78
Figure 3.2. Accumulated sales, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 1997.....	78
Figure 3.3. Accumulated operating profits, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 1997	78
Figure 3.4. Accumulated R&D spending, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies in 2003.....	81
Figure 3.5. Accumulated sales, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 2003.....	81
Figure 3.6. Accumulated operating profits, actual, adjusted, and optimized	

number of NMEs among Japanese pharmaceutical companies from 1980 to 2003	82
Figure 3.7. Accumulated R&D spending, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies in 2006.....	84
Figure 3.8. Accumulated sales, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 2006.....	85
Figure 3.9. Accumulated operating profits, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 2006	85
Figure 3.10. Separate R&D productivity map in 1997	92
Figure 3.11. RDP map in 1997	93
Figure 3.12. Separate R&D productivity map in 2003	94
Figure 3.13. RDP map in 2003.....	94
Figure 3.14. Separate R&D productivity map in 2006	95
Figure 3.15. RDP map in 2006.....	96
Figure 3.16. Trends of MI indices of the R&D productivity grouped by antibiotics development strategy	102
Figure 3.17. Trends of MI indices of the R&D productivity grouped by subclass.....	103
Figure 4.1. Accumulated R&D spending, actual number and optimized number of NMEs of global pharmaceutical companies in 2007.....	111
Figure 4.2. Actual number and optimized number of NMEs, accumulated net present value of global pharmaceutical companies in 2007	111

Figure 4.3. Accumulated R&D spending, actual number and optimized number of NMEs of global pharmaceutical companies in 2012.....	114
Figure 4.4. Actual number and optimized number of NMEs, accumulated net present value of global pharmaceutical companies in 2012	114
Figure 4.5. Separate R&D productivity map of global pharmaceutical industry in 2007	118
Figure 4.6. RDP map of global pharmaceutical industry in 2007	118
Figure 4.7. Separate R&D productivity map of global pharmaceutical industry in 2012	119
Figure 4.8. RDP map of global pharmaceutical industry in 2012	120

List of Tables

Table 1.1. Major pharmaceutical industry consolidations between 1995 and 2012	21
Table 1.2. Top 10 M&A transactions by transaction amount between 2008 and 2012.....	22
Table 1.3. List of Japanese originated ethical drugs available over 20 countries in 1980s and 1990s.....	29
Table 2.1. DEA models used for R&D Productivity measures	42
Table 2.2. Comparison of four models for R&D productivity measures using DEA	46
Table 2.3. List of variables used for Japanese and global pharmaceutical industries.....	54
Table 2.4. Financial data and the number of NMEs approved from 1980 to 1997	55
Table 2.5. Japanese pharmaceutical drug production amount from 1976 to 1997 and its production share by therapeutic categories.....	57
Table 2.6. Trends of Japanese ethical drug approved by franchise category from 1980 to 1997	58
Table 2.7. List of domestic approved NMEs by company	59
Table 2.8. Therapeutic development strategy by company from 1980 to 1997	60
Table 2.9. Accumulated R&D spending, actual and adjusted number of NMEs, accumulated sales, and accumulated operating profits for Japanese companies from 1980 to 1997	61
Table 2.10. Accumulated R&D spending, actual and adjusted number of NMEs,	

accumulated sales, and accumulated operating profits for Japanese companies from 1980 to 2003	61
Table 2.11. Accumulated R&D spending, actual and adjusted number of NMEs, accumulated sales, and accumulated operating profits for Japanese companies from 1980 to 2006	62
Table 2.12. List of ethical drugs developed from 1980 to 1999 with sales above 30 billion yen in 2010.....	63
Table 2.13. Industry consolidations of the Japanese pharmaceutical industry	65
Table 2.14. Financial, number of NMEs and net present value by origin of the company in 2007 (unit: billion us dollars)	68
Table 2.15. Financial, number of NMEs and net present value by origin of the company in 2012(unit: billion us dollars)	70
Table 2.16. Comparison of NMEs by company and therapeutic category in 2007	71
Table 2.17. Comparison of NMEs by company and therapeutic category in 2012	72
Table 3.1. Comparison of DEA scores of 15 Japanese companies in 1997	76
Table 3.2. Comparison of the actual, adjusted and optimized number of NMEs for each Japanese company in 1997.....	77
Table 3.3. Comparison of DEA scores of 15 Japanese companies in 2003	80
Table 3.4. Comparison of the actual number of NMEs with the optimized number of NMEs for each company in 2003.....	80
Table 3.5. Comparison of DEA scores of 15 Japanese companies in 2007	83
Table 3.6. Comparison of the actual number of NMEs with the optimized number of NMEs for each company in 2006.....	84

Table 3.7. MI score of the R&D productivity for 15 Japanese companies from 1980 to 1997 by company	86
Table 3.8. EC score of the R&D productivity for 15 Japanese companies from 1980 to 1997 by company	87
Table 3.9. FS score of the R&D productivity for 15 Japanese companies in 1997	88
Table 3.10. Statistical results on relationships between R&D productivity and industry consolidation	89
Table 3.11. Statistical results on the R&D productivity using the MI scores	90
Table 3.12. Statistical results on antibiotics development strategy by style	90
Table 3.13. Statistical results on antibiotics development strategy by subclass ..	90
Table 3.14. Statistical results on relationships between R&D productivity and therapeutic categories in 1997.....	91
Table 3.15. Average score of MI Index and its components, with subgroups defined by the company's antibiotics development strategy	101
Table 4.1. ROI and R&D productivity scores under several DEA models in 2007	108
Table 4.2. Comparison between the actual number of NMEs and the optimized number of NMEs in 2007	110
Table 4.3. ROI and R&D productivity scores under three DEA models in 2012..	112
Table 4.4. Comparison between the actual number of NMEs and the optimized number of NMEs in 2012	113
Table 4.5. Statistical results on R&D productivity scores and industry consolidations	115

Table 4.6. Mann-Whitney U test results on five major therapeutic category and R&D productivity components in 2007	116
Table 4.7. Mann-Whitney U test results on five major therapeutic category and R&D productivity components in 2012	117
Table 4.8. R&D productivity ranking in 2007 and 2012.....	121
Table 4.9. Cancer drugs under development by therapeutic modality	126

Abstract

Analysis of research and development (R&D) productivity of the pharmaceutical industry has increased. A pharmaceutical company needs to improve R&D productivity to sustain earnings and some papers argue the decline of R&D productivity is a cause of mergers and acquisitions (M&A). A conventional method for measuring R&D productivity on an individual company basis is based on R&D efficiency, i.e., a ratio of R&D spending to number of successful new molecular entities (NMEs), and there are limitations to examining relationships between R&D productivity and industry consolidation. Few methods incorporate the nature of the pharmaceutical industry, including differences in therapeutic category risk profiles, and measure R&D productivity on an individual company basis. The goal of this dissertation is to develop a novel method to measure R&D productivity of an individual pharmaceutical company incorporating industry characteristics. Based on these outcomes, relationships between R&D productivity and industry consolidation and between R&D productivity and therapeutic categories are investigated.

Out of 24 publicly listed Japanese companies since 1980, 15 are selected using one input variable (actual R&D spending) and three output variables (accumulated number of weighted NMEs, sales, and operating profit). The weight is assigned based on development stage using an interview form

regarding R&D spending: 50% for in-licensed NME and 20% for co-development NME. Annual reports from 1970 to 1997 are used for financial information and 1997 is the endpoint because it marks the end of the non-M&A period.

Out of 50 global pharmaceutical companies including seven Japanese pharmaceutical companies, 21 are selected and three variables are employed: R&D spending, number of NMEs, and aggregated net present value (NPV). R&D spending is obtained from annual reports from 2002 to 2012. We include 604 NMEs in the data set that were engaged in a Phase III study initiated between 2002 and 2007 or between 2008 and 2012 (using annual reports). NPVs of 21 global pharmaceutical companies from Pharmapipeline® were obtained from Barclays Capital. The data collection endpoint is 2007 because it marks a period just before several large M&A transactions.

To visualize company R&D productivity among industry peers, a relative ranking approach is used to eliminate an impact on size effect. This approach is based on data envelopment analysis (DEA) since DEA is based on distance from the efficiency frontier constructed from optimal companies. The Malmquist index is employed to identify historical R&D productivity changes in Japanese companies from 1980 to 1997.

We deconstruct R&D productivity into two components: cost efficiency (number of NMEs divided by R&D spending) and product value effectiveness (product value divided by number of NMEs). Based on these scores, a benchmark is constructed that employs two-stage DEA. An advantage of using two-stage DEA is the ability to measure overall R&D productivity. The cost efficiency index (number of optimized NMEs divided by R&D spending) and product value effectiveness index (product value divided by number of optimized NMEs) for each company are measured. The optimized number of NMEs minimizes the difference between two indices to estimate overall optimal R&D productivity. A R&D productivity map (RDP map) is constructed using the cost efficiency index (x-axis of the map) and product value effectiveness (y-axis).

Results using the Malmquist index indicate that the R&D productivity of the 15 Japanese companies declined and that there is dispersion of R&D productivity deterioration. RDP map results illustrate that companies with optimal cost efficiency ($p < 0.05$) merged with companies with the least-optimal product value effectiveness ($p < 0.10$). The four largest therapeutic franchises have optimal product value effectiveness ($p < 0.01$), companies involved in antibiotics have optimal cost efficiency ($p < 0.1$), and companies involved in lifestyle diseases have the least-optimal cost efficiency ($p < 0.001$). Selection of a particular franchise may lead to

deterioration of R&D productivity in the future.

Results indicate that out of 21 companies in 2007, 11 had optimal cost efficiency, two had optimal product value effectiveness, and one company had both. Companies with lower cost efficiency scores were more likely to actively engage in M&A ($p < 0.05$) in 2007. Results indicate that in 2012, one company had optimal cost efficiency, two had optimal product value effectiveness, and no company had both. This dissertation also illustrates the cause of M&A among pharmaceutical companies, which was not explained by previous literature.

Statistical results indicate companies involved in vaccines were less cost efficient ($p < 0.001$) and those involved in the central nervous system (CNS) had the least product value effectiveness ($p < 0.001$). In 2012, companies that developed cancer and respiratory therapies ($p < 0.001$) were less cost efficient. Franchise selection criteria may vary among companies but the criteria impacts future R&D productivity.

Based on these results, at least two suggestions to the pharmaceutical industry can be presented. First, to sustain R&D productivity over the long term, companies should focus on dominant therapeutic franchises and balance cost efficiency with product value effectiveness. Second, if a company becomes least optimal or fails significantly to catch up with the

benchmark, pursuing M&A may no longer solve the decline of R&D productivity. As companies seek economies of scale and become successful, R&D spending increases and the sustainability issue arises. Companies have at least three options: 1) devote to potentially high-value products with high failure risk, 2) diversify therapeutic categories, and 3) collaboration.

The R&D productivity model and map measure an individual company's R&D productivity with two dimensions to visualize relative status in the pharmaceutical industry, and to indicate a possible solution to improve R&D productivity. While there are several useful R&D management tools, the RDP map provides another way to inspect current R&D strategy. The map shows how to improve productivity by either complementing cost efficiency or product value effectiveness, or both.

1 Introduction

The goal of this dissertation is to develop a novel method to measure research and development (R&D) productivity of an individual pharmaceutical company, incorporating industry characteristics such as the relationship between R&D spending and the number of new molecular entities (NMEs) developed. Based on these outcomes, relationships between R&D productivity and industry consolidation and between R&D productivity and therapeutic categories are investigated. With this model, management can measure relative R&D productivity status among industry peers and possibly identify strategic initiatives to improve company R&D productivity. There are many methods to measure R&D productivity but few incorporate the nature of the pharmaceutical industry, which includes risk profile differences of therapeutic categories, and measure R&D productivity on an individual company basis.

1.1. Research background

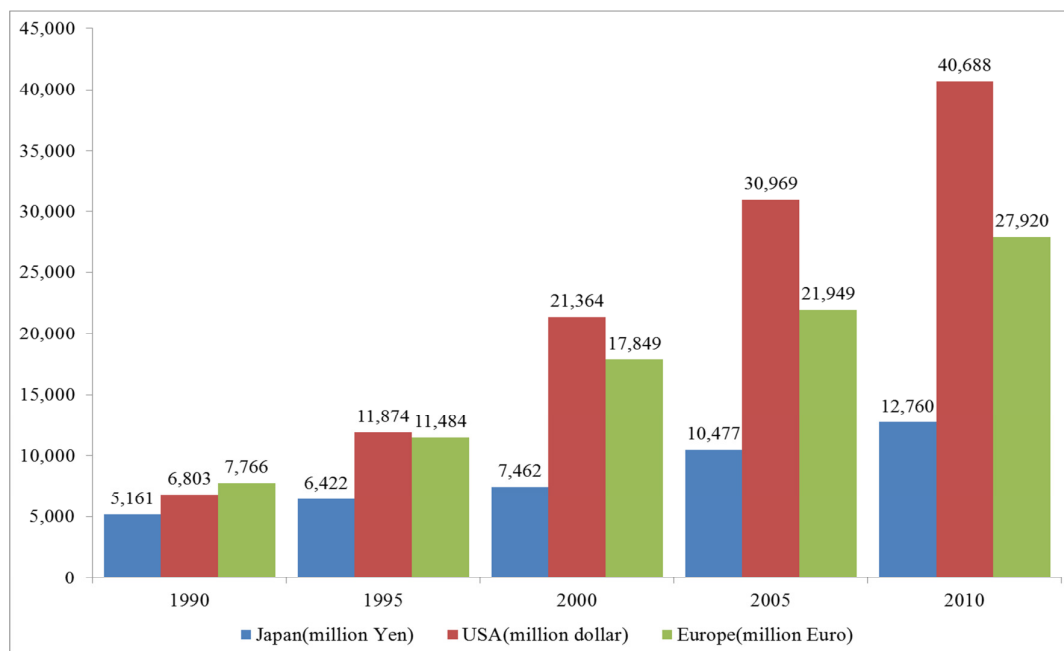
In this introduction, first, deterioration of R&D productivity and resulting industry consolidation is explained. Second, based on previous literature, research gaps are identified and the purpose of this dissertation is explained in order to fill these gaps.

1.1.1. Deterioration of the R&D productivity in the pharmaceutical industry

Although R&D spending in the pharmaceutical industry has increased rapidly [1-3], the number of NMEs has declined in recent decades [4-6]. Scannell et al. argue that the significant advances in science and technology can enhance R&D productivity. However, the ratio of NMEs to R&D spending has declined by roughly 50% every nine years since 1950 [7]. Some studies suggest development risk remained relatively stable between the 1970s and 1990s [8-10], but clinical trials became more complex and more expensive [6].

Among Japan, Europe, and the United States, R&D spending declined most in Japan [11]. As Figure 1.1 illustrates, Japanese companies spent 5.2 billion yen in 1990 and 12.8 billion yen in 2010; the compound annual growth rate (CAGR) was 2.1%. US companies spent 6.8 billion dollars in 1990 and 40.7 billion dollars in 2010 (8.8% CAGR). European companies spent 7.8 billion euros in 1990 and 27.8 billion euros in 2010 (5.1% CAGR).

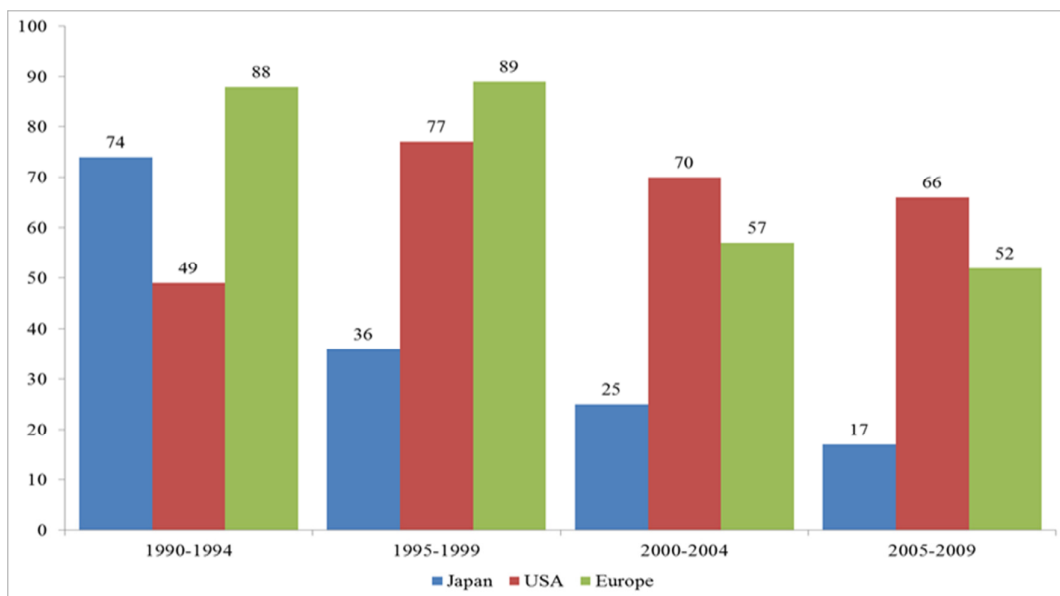
Figure 1.1. Historical trends of R&D spending and NMEs by region



Source: European Federation of Pharmaceutical Industries and Associations, 2010 Edition [12]

R&D productivity in terms of NME development declined most in Japan. Japanese, US, and European pharmaceutical companies developed 74, 49, and 88 NMEs, respectively, between 1990 and 1994, and 17, 66, and 52 NMEs between 2005 and 2009 (Figure 1.2). This implies the level of innovation in the Japanese pharmaceutical industry between 2005 and 2009, measured by number of NMEs, was 22% of the level between 1990 and 1994.

Figure 1.2. Historical trends of NMEs by region



Source: European Federation of Pharmaceutical Industries and Associations, 2010 Edition [12]

As a result, productivity of pharmaceutical company R&D has recently received increased scholarly attention. Specifically, increases in R&D spending, and imposition from regulatory hurdles and fiscal austerity measures, have created an environment in which the pharmaceutical industry must strive to overcome deterioration of R&D productivity. [9-14].

1.1.2. Industry consolidation in the pharmaceutical industry

The decline of R&D productivity and changes in the business environment are widely considered to have been critical drivers of Mergers and Acquisitions (M&A) in recent years [2, 15-16]. The first major example of industry consolidation was observed in 1995 when Glaxo and Wellcome

merged to become the largest British pharmaceutical company. There was no major industry consolidation in Japan until 1998 and there have been several industry consolidation events among large global pharmaceutical companies since 1995 (Table 1.1).

Table 1.1. Major pharmaceutical industry consolidations between 1995 and 2012

	Japan			Global		
	Companies		Merged company	Companies		Merged company
1995				Glaxo	Wellcome	Glaxo Wellcome
				Pharmacia	Upion	Pharmacia
1996				Sandoz	Ciba-Geigy	Novartis
1997						
1998	Yoshitomi	Green Cross	Yoshitomi			
1999	Mitsubishi Chemical	Tokyo Tanabe	Mitsubishi Chemical	Zeneca	Astra	AstraZeneca
1999				Pfizer	Warner Lambert	Pfizer
	Boehringer	Mitsui Pharma	Boehringer	Hoechst	Rhone-Poulenc	Aventis
2000				Smith Kline	Glaxo Wellcome	GSK
				Pharmacia	Monsant	Pharmacia
2001	Roche	Chugai	Roche			
2002	Taisho	Toyama Kagaku	Subsidiary of Taisho	Pfizer	Pharmacia	Pfizer
2003	Merck	Banyu	Merck			
2004				Sanofi	Synthe-labo	Sanofi
				Sanofi	Aventis	Sanofi
2005	Yamanouchi	Fujisawa	Astellas			
	Sumitomo Chemical	Dainippon	Dainippon Sumitomo			
2006						
2007	Daiichi	Sankyo	Daiichi Sankyo			
2007	Mitsubishi Chemical	Tanabe	Tanabe Mitsubishi			
	Takeda	Millennium	Takeda	Roche	Genetech	Roche
2008	Daiichi Sankyo	Ranbaxy	Subsidiary of Daiichi Sankyo			
	Eisai	MG Pharma	Eisai			
2009	Dainippon Sumitomo	Sepracor	Dainippon Sumitomo	Pfizer	Wyeth	Pfizer
				Merck	Schering Plough	Merck
				Sanofi	Genzyme	Sanofi
2010	Astellas	OSI	Astellas	Novartis	Alcon	Novartis
				Gilead Science	Pharmasset	Gilead Science
2011	Takeda	Nycomed	Takeda			
2012	Takeda	URL Pharma	Takeda	Sanofi	Amylin	Sanofi

Source: company annual reports

Press releases from the top 50 global pharmaceutical companies in terms of sales suggest 79 M&A transactions occurred between 2008 and 2012 and these transactions total 388 billion dollars in value. Table 1.2 illustrates the top 10 M&A transactions by transaction amount between 2008 and 2012. These 10 transactions, totaling 193 billion dollars, represent 49.7% of the total value of all M&A transactions between 2008 and 2012. With the

exception of two cases, the acquisition of Synthes (medical equipment company) by Johnson and Johnson and the acquisition of Barr Pharmaceuticals (a generic drug company) by Teva Pharmaceuticals, all transactions involved the takeover of research-oriented pharmaceutical companies. Consequently, to address the deterioration of R&D productivity, Japanese pharmaceutical companies started pursuing M&A by targeting overseas companies.

Table 1.2. Top 10 M&A transactions by transaction amount between 2008 and 2012

Date	Companies	Amount (US million dollars)	
2009/01	Pfizer	Wyeth	68,000
2008/07	Roche	Genentech	46,800
2009/03	Merck & Co	Schering-Plough	41,000
2011/04	Johnson & Johnson	Synthes	21,300
2010/08	Sanofi-Aventis	Genzyme	20,100
2011/05	Takeda Pharmaceutical	Nycomed	13,684
2010/01	Novartis	Alcon Laboratories	12,900
2011/11	Gilead Sciences	Pharmasset	11,000
2008/04	Takeda Pharmaceutical	Millennium	8,800
2008/07	Teva	Barr Pharmaceuticals	7,460

Source: company annual reports and press releases

As R&D productivity has declined among pharmaceutical companies, the companies have struggled to improve R&D productivity and one way to improve has been M&A [17]. A conventional method for measuring R&D productivity on an individual basis is based on R&D efficiency (i.e., ratio of R&D spending to successful number of NMEs), but there are some limitations to examining the relationships between R&D productivity and industry consolidation using this outcome alone. A multidimensional

measure for analyzing the R&D productivity of an individual company would enable management to improve their overall R&D strategy.

1.2. Literature review

This section reviews previous literature on R&D productivity and consolidation in the pharmaceutical industry to verify research gaps.

1.2.1. Previous literature on R&D productivity in the pharmaceutical industry

In general, R&D productivity is measured by the amount of R&D spending required in a particular year to generate the same level of output. Measuring R&D productivity is not an easy task because the selection of methodology and appropriate variables is crucial. For example, Geier [18] and, Brown and Svenson [19] use a single source output, and Hashimoto and Haneda [20] measure R&D productivity by accumulated R&D spending over 8 years using a single input and three outputs: number of patents, revenue, and operating profit. These papers use the number of patent and publication submissions as input variables to measure R&D productivity and this creates an issue because these variables do not necessarily support NME production and subsequent product launches.

Another conventional approach for measuring R&D productivity is to divide aggregated NPV of a company's NMEs by total R&D spending to calculate return on investment (ROI), which illustrates the value of NME per dollar

spent on R&D. Despite its utility, the inherent weakness of ROI analysis is that a company's relying on a few profitable drugs is not measured. For example, a company could have a high overall ROI but that ROI may be dependent on a few key, profitable products; after patents for those key drugs expire, the company's ROI could drop substantially. The model falls short of measuring overall R&D productivity.

Elebring et al [21] suggest a balance between effectiveness and efficiency, i.e., between R&D speed, cost, and quality is important. They also emphasize the importance of selecting appropriate metrics because choosing too many metrics, and/or the wrong metric, could adversely affect the effectiveness. Empfield and Leeson [22] also explain the potential risk of measuring R&D productivity based on cost efficiency alone: awarding scientists by the number of drug projects that passed the milestone results in too many live projects in the pipeline.

To overcome weaknesses associated with a typical ratio analysis (such as ROI), Paul et al [23] argue that R&D productivity can be deconstructed into two constituent ratios: R&D efficiency and R&D effectiveness. They define R&D efficiency as company cost per NME, and R&D effectiveness as company value per NME, and they express R&D productivity as a ratio: the numerator includes the number of products under clinical trial, transitional probabilities, and value, and the denominator accounts for time and

spending associated with clinical trials. Their economic model indicates that the cost of discovering and developing an NME is a principal contributor to rising R&D spending. To measure R&D productivity, an idea introduced by Paul et al. would be ideal except that their model also falls short of explaining impacts from each stage of overall R&D productivity, and it is not on an individual company basis.

Some studies focus on estimating new drug development for clinical trial stages and certain therapeutic categories as a part of R&D productivity measures. Morgan et al [24] suggest no gold standard exists to estimate drug development costs, while DiMasi et al [25] estimate that the average cost of new drug development is 466 million dollars per approved drug based on clinical trial spending for 68 drugs from 10 large pharmaceutical companies from 1983 to 1994. DiMasi et al. also estimate costs for cardiovascular (460 million dollars), CNS (464 million dollars), anti-infective (492 million dollars), and analgesic/anesthetic drugs (375 million dollars), and the mean NPV of lifecycle sales for cardiovascular (3.7 billion dollars), CNS (4.2 billion dollars), anti-infective (2.2 billion dollars), and analgesic/anesthetic drugs (1.1 billion dollars) for the first half of the 1990s (average sales of 2.4 billion dollars). They conclude that R&D efforts would shift toward high net return areas and away from lower net return, therapeutic areas. Adam and Brantner [26] also estimate the cost for eight

therapeutic categories using data from 1989 to 2002. They find that estimates vary depending on the therapy: CNS (1.1 billion dollars), anticancer (1.0 billion dollars), blood (906 million dollars), and cardiovascular (887 million dollars) were higher than the average cost of 868 million dollars based on 1,682 observations; biological drugs are not estimated separately. When R&D productivity measurement is considered, it is important to pay careful attention to therapeutic categories that companies develop. Notably, while selection of therapeutic categories plays an important role in R&D product development strategy, there is limited multidimensional research on the relationship between R&D productivity and therapeutic categories.

1.2.2. Previous literature on industry consolidation in the pharmaceutical industry

Considerable research examines reasons for industry consolidation including acquisition of specific assets and a response to excess capacity. Higinis and Rodriguez [27] find that mergers are a means to outsource R&D using a “desperation index,” which includes expected years of patent life. Danzon et al [28] examine the determinants and effects of M&A and finds that mergers by large companies are a response to expected capacity due to patent expirations and gaps in a company’s product pipeline, while mergers are primarily an exit strategy in response to financial trouble. Some papers

question whether value is created through industry consolidation within the pharmaceutical industry. For example, Andrade et al [29] compare companies' operating margins, before and after mergers, to the industry average, and conclude that no underlying gain from mergers can be identified. Some papers (i.e., Ravenscraft and Long [1]) analyze industry consolidation events from the stock market's viewpoint and provide mixed results. Considerable research analyzes industry consolidation from the industry's viewpoint rather than from companies' viewpoint.

Regarding relationships between R&D productivity and determinants of industry consolidation, few research studies employ product value regarding sales, operating profits, and NPV of compounds in conjunction with developed or launched NMEs. Demirbag [31] finds that no value was created in the sample M&A transactions regarding R&D productivity, ROI, and profit margin, with R&D productivity defined as the ratio of total number of NMEs developed divided by total R&D spending within a five-year timeframe. Ornachi [32] finds that merged companies have, on average, worse performance than non-merged companies, using R&D spending and number of patents to measure R&D productivity. Danzon et al [28] investigate reasons for M&A using excess capacity due to pipeline gap; they use three variables: Tobin's q, percentage of lagging sales, and percentage of a firm's marketed drugs approved by the FDA for between 9

and 14 years. These indicators are valid proxies but fall short of explaining relationships between R&D productivity and determinants of industry consolidation because there is no evaluation of the current pipeline.

Several papers discuss changes in R&D productivity among Japanese pharmaceutical companies. The Japanese pharmaceutical industry has contributed many innovative drugs to the global market (Table 1.3): 14 NMEs during the 1980s and 16 new NMEs during the 1990s. Eight out of 14 NMEs sold globally during the 1980s, and four out of 16 during the 1990s, were antibiotics. Japan is considered one of the top antibiotic developers in the world. In 2007, three out of the top five global antibiotics in term of sales were originally developed by Japanese companies. This impressive antibiotics development was rooted in the R&D programs of the 1980s.

Table 1.3. List of Japanese originated ethical drugs available over 20 countries in 1980s and 1990s

Year of Domestic approval	Company	Generic name	Category	Sales in FY2010 (billion yen)
1978	Eisai	Mecobalamin	Vitamin B12	30.4
1985	Yamanouchi	famotidine	Digestive drug	41.7
1986	Sankyo	Loxoprofen Sodium Hydrate	Inflammatory drug	54.2
1987	Seikagaku/Kaken	Sodium hyaluronate	Joint dysfunction drug	30.8
1988	Otsuka	Cilostazol	Antiplatelet drug	46.5
1988	Ono	Limaprost alfadex	Hormone	40.1
1998	Hisamitsu	Ketoprofen	Inflammatory patch	86.4
1989	Sankyo	pravastatin sodium	Cholesterol lowering drug	38.1
1990	Chugai	Epoetin Beta	Anemia	40.0
1990	Mochida	Ethyl icosapentate	Cholesterol lowering drug	37.0
1992	Takeda	lansoprazole	Digestive drug	70.9
1992	Takeda	Leuprorelin Acetate	Cancer drug	65.9
1993	Fujisawa	Tacrolimus	immunosuppressive drug	39.6
1993	Daiichi	levofloxacin	Antibiotics	32.4
1994	Takeda	Voglibose	Diabetics drug	32.2
1995	Ono	Pranlukast Hydrate	Asthma	30.0
1997	Eisai	Rabeprazole	Digestive drug	60.2
1999	Takeda	Candesartan	Hypertension drug	122.9
1999	Takeda	Pioglitazone hydrochloride	Diabetics drug	122.9
1999	Eisai	Donepezil	Digestive drug	93.6
1999	Taiho	Tegafur	Anticancer drug	37.1

Source: company annual reports

After a series of successful drug developments during the 1980s and early 1990s, the Japanese industry started to deteriorate. There is considerable research that explains changes in the Japanese pharmaceutical industry during these periods [33-34]. Thomas [35] argues the Japanese domestic environment for pharmaceuticals changed radically from 1975 to 1995, and resulted in degradation of innovative capability for Japanese drug companies. Mitchell et al. [36] also study changes in R&D spending of

Japanese pharmaceutical manufacturers between 1975 and 1990, and stress the importance of understanding dynamics of R&D investment strategies. Mahlich [33] provides evidence that international patents contribute to firms' market value expressed in Tobin's q , while the publication did not. Hashimoto and Haneda [20] also observe that the R&D efficiency of Japanese pharmaceutical companies deteriorated from 1983 to 1992 by employing data envelopment analysis (DEA). They measure R&D efficiency using accumulated R&D spending over 8 years as a single input and number of patents, revenue, and operating profits as outputs. There is considerable research regarding the decline of R&D productivity, but few studies analyze the relationship between the decline of R&D productivity and industry consolidation.

In summary, there are many approaches to evaluate R&D productivity but few consider pharmaceutical industry characteristics, such as the relationship between R&D spending and number of NMEs developed, and risk/return profiles of therapeutic categories. To consider the uniqueness of pharmaceutical R&D productivity, a new approach would be more appropriate than an absolute measurement approach. Furthermore, there is limited multidimensional research that examines R&D productivity on an individual company basis, and factors associated with industry consolidation, by employing the multi-dimension approach. Few studies

quantitatively investigate the possible causes of deterioration and the relationship between deterioration and M&A.

1.3. Purpose of the dissertation

This dissertation attempts to address gaps in the literature by utilizing available quantitative approaches to examine relationships between R&D productivity, industry consolidation, and therapeutic categories. This is the first attempt to develop a R&D productivity measure to visualize R&D productivity status on an individual company basis and to analyze these relationships. To accomplish the task, first, a new R&D productivity method must be established to measure R&D productivity of an individual company, deconstructing R&D productivity into two factors: cost efficiency and product value effectiveness. Cost efficiency represents how a company efficiently produces an NME given R&D spending, and product value effectiveness represents how a company effectively increases product value (sales and operating profit) given number of NMEs produced. For each factor of R&D productivity, a score relative to the industry benchmark is calculated based on the DEA approach [38]. This method enables visualization of R&D productivity for each company, relative to the pharmaceutical industry, and investigates the quality of corporate behavior in this domain.

Second, based on outcomes of these measures, relationships between R&D

productivity and industry consolidation and between R&D productivity and therapeutic franchises are investigated. To illustrate these relationships, the Japanese pharmaceutical industry from 1980 to 1997 and in 2003 and 2006, and the global pharmaceutical industry in 2007 and 2012 are employed. For the Japanese case, additional studies are also conducted to investigate relationships between the decline of R&D productivity and industry consolidation, and interactions between R&D productivity and therapeutic categories.

Improvement of R&D productivity has been a crucial management issue for pharmaceutical companies. This dissertation attempts to measure and visualize R&D productivity of an individual company by deconstructing productivity into two factors, and verify relationships between R&D productivity and industry consolidation and between R&D productivity and therapeutic categories. In turn, recommendations to pharmaceutical company managements and the industry are provided based on findings from this dissertation.

1.4. Organization of the dissertation

This dissertation is composed of five chapters. Chapter 1 describes the purpose of the dissertation and presents the research question, given the urgent needs of analyzing productivity of pharmaceutical R&D, regarding multiple dimensions and relationships among R&D productivity, industry

consolidation, and therapeutic categories. Chapter 1 also reviews previous literature on R&D productivity measures and industry consolidation among pharmaceutical companies to verify if such research has been conducted. Chapter 2 provides methodologies employed in this dissertation, and provides deep coverage of methodology because the new measurement tool for R&D productivity using the two-stage DEA and RDP map is developed. In addition, the Malmquist index is utilized to measure deterioration of R&D productivity among Japanese companies to verify a relationship between R&D productivity and industry consolidation on an individual basis, and between R&D productivity and therapeutic categories. Since Japanese pharmaceutical companies from 1980 to 2006 and global pharmaceutical companies from 2003 to 2012 are both examined, detailed descriptions of each group are provided. Chapter 3 discusses Japanese pharmaceutical companies, with a particular focus on relationships between R&D productivity and industry consolidation and between R&D productivity and therapeutic categories. Chapter 4 discusses global pharmaceutical companies, regarding relationships between R&D productivity and industry consolidation and between R&D productivity and therapeutic categories. Chapter 5 discusses results from two different universes and provides recommendations. At the end, limitation of scope, future research topics, and the conclusion are provided. Appendices

illustrate key data sets employed in this dissertation.

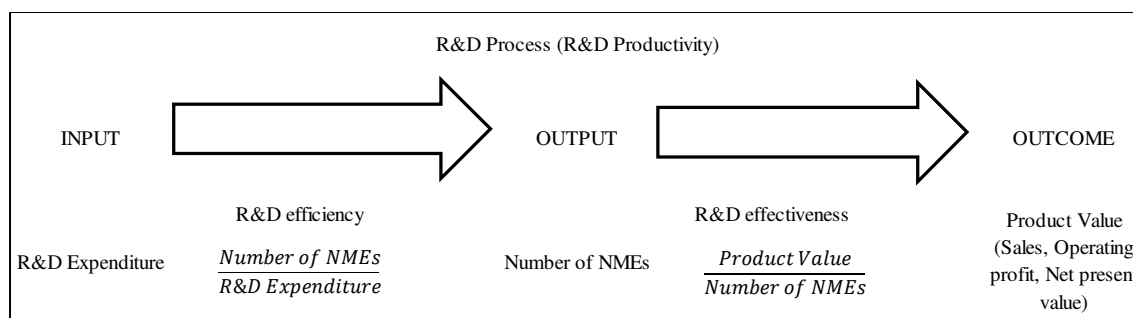
2. Methodology/Data

Chapter 2 provides methodologies and data that are employed in this dissertation. This chapter explains rationales to choose DEA approach and other methods. Detailed descriptions on both Japanese pharmaceutical companies and global pharmaceutical companies are provided.

2.1. Definition of R&D productivity in this dissertation

In general, the R&D productivity of a pharmaceutical company is measured by calculating the amount of R&D spending required in a particular year to generate the same output level as produced in the same year; however, measure the R&D productivity is not an easy task since selection of methodology and appropriate variables are crucial [39]. As the potential risk of R&D productivity measure based on the cost efficiency alone was previously discussed [22], an important reason to decompose the R&D productivity is to identify an inherent risk which the conventional productivity cannot detect the company with small number of high value products. Paul et al. [23] argue that R&D productivity can be decomposed into two constituent ratios: R&D efficiency and R&D effectiveness (Figure 2.1) to overcome this issue. They define R&D efficiency as a ratio of the number of NMEs to R&D spending and R&D effectiveness as product value per the number of NMEs. Examples of product value are sales, operating profit, and the net present value (NPV) of the NMEs.

Figure 2.1. Schematic view on R&D productivity by Paul et al



Source: modified from Paul et al. [2]

A drawback on their research is that their model is short of explaining individual company's R&D productivity and its constituents. In order to incorporate the industry characteristics of the pharmaceutical industry and to measure R&D productivity on an individual company basis, a relative measurement approach based on their approach would be more appropriate. In order to measure the individual company's R&D productivity incorporating the nature of the pharmaceutical industry, a method can be established by utilizing efficient frontiers, or a set of benchmarks for both R&D efficiency and effectiveness since it is possible to measure relative inefficiency (a distance) of the individual company from its benchmark.

As a first step to construct the efficient frontier, R&D efficiency employing R&D spending, and the number of NMEs, and R&D effectiveness employing the number of NMEs and product values are calculated for every company. Based on these outcomes, benchmark companies are identified. It is possible to measure the R&D productivity using this efficient frontier on individual

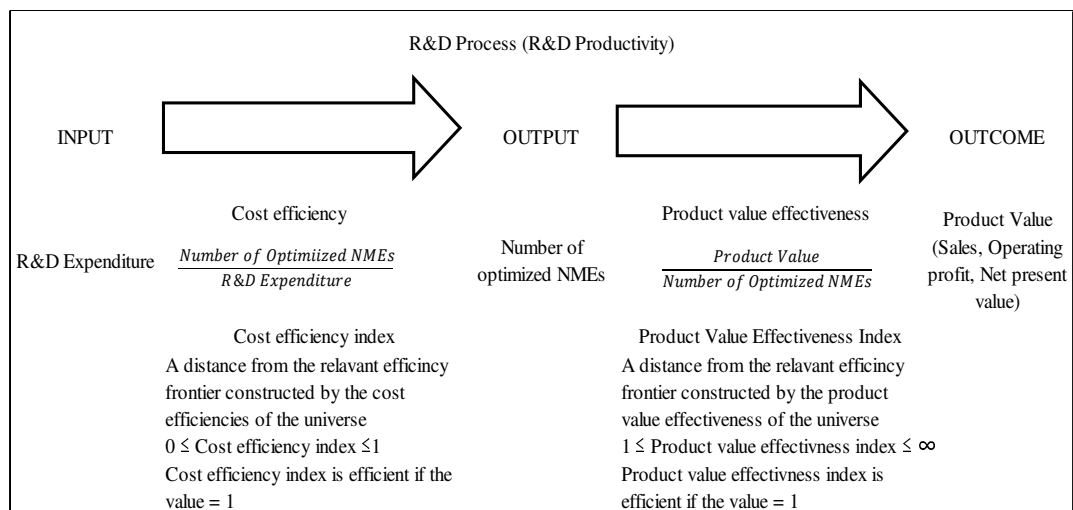
company basis, some studies argued to an intermediary should be employed in order to measure the overall R&D productivity [40-41]. This intermediary is also an output from the R&D efficiency and sole input variable to the R&D effectiveness. In this dissertation, this intermediary is defined as the optimized number of NMEs.

Cost efficiency is defined as a ratio of the optimized number of NMEs to R&D spending and product value effectiveness is defined as product value per the optimized number of NMEs. Since the optimized number of NMEs minimizes the distance of the individual company's cost efficiency and product value effectiveness from its benchmark, outcomes are guaranteed to achieve the most optimal R&D productivity given its variables.

Finally the distance of individual company's R&D cost efficiency from the relevant efficiency frontier is measured and this distance is called a cost efficiency index. The value ranges from 0 and 1. The most cost efficient company receives the cost efficiency index of 1; otherwise, the index will be less than 1. Figure 2.2 illustrates a schematic view on R&D productivity used in this dissertation. For example, if the company produces 5 NMEs using 5 million dollars in R&D spending and the company is considered as a benchmark, the cost efficiency index of 1 is received. If another company produces 5 NMEs using 10 million dollars in R&D spending, the company receives its cost efficient index of 0.5 or 50% worse off than the benchmark.

The distance of individual company's R&D product value effectiveness from the relevant benchmark is measured and this distance is called a product value effectiveness index. The value ranges from 1 and infinity. The most product value effective company, a benchmark, receives the product value effectiveness index of 1; otherwise, the index will be greater than 1. For example, if the company produces 5 NMEs and its aggregated NPVs are 50 million dollars and the company is considered as a benchmark, its product effectiveness index will be 1. If another company produces 10 million dollars in NPVs with 5 NMEs, the company receives its product effectiveness index of 5 or 500% worse off than the benchmark.

Figure 2.2. Schematic view on R&D productivity used in this dissertation



2.2. Data envelopment analysis

In general, there are at least four approaches to measuring R&D productivity: ratio analysis, econometric model, stochastic frontier analysis,

and DEA. DEA is originally developed by Charnes et al [42] and has been employed as an effective tool in identifying empirical frontiers and in evaluating relative efficiency [18, 37, 40, 42]. While DEA is selected as the most appropriate method to measure the pharmaceutical company's R&D productivity, rationales are as follows. Ratio-based analysis is the simplest approach and produces information on the relationships between single input and output. When a multiple number of ratios are employed, it is possible to standardize ratios. The weakness is that one cannot pinpoint a consistent benchmark incorporating all inputs and outputs. DEA is able to handle multiple inputs and outputs simultaneously. This ratio analysis is often used as a fundamental method in performance evaluation this measure can suffice for the purpose of performance evaluation. Particularly, the use of single measures ignores any interactions, substitutions or tradeoffs among various performance measures. Each business operation has specific performance measures with tradeoffs. Another drawback is that the ratio analysis cannot employ multiple variables at the same time.

The econometric model, the least-squares regression method, is a popular parametric method with multiple inputs and outputs. The fundamental difference between the econometric and DEA approaches is that the former reflects the average or central tendency behavior of the observations, while the latter deals with the best performance and evaluates all performances

by deviations from the efficient frontier. To estimate the efficient frontier, optimization techniques are often applied. DEA offers at least two advantages as an empirical tool in measuring R&D efficiency. First, it does not require a data normalization process, unlike in an econometric approach. Second, it is a non-parametric approach and does not require an explicit specification of inputs and outputs.

Stochastic frontier analysis is also a parametric method using a concept of efficient frontier. A difference between econometric model and stochastic frontier analysis that the former assumes that all firms are efficient but the latter assume that all firms are not efficient. Even though stochastic frontier analysis is superior but has some drawbacks. Stochastic frontier analysis utilizes the functional forms but there is no such information for measuring the pharmaceutical company's R&D productivity. Thus, an empirically estimated efficient frontier based on the observations should be considered.

There are at two general DEA models to construct the efficient: input-oriented and output-oriented models. The input-oriented model is to minimize the inputs while the outputs remain at their current level while the output-oriented model is to maximize the output while the input remains at their current level [42, 44]. In our study, the input-oriented model is employed to construct a cost efficiency frontier and the

output-oriented is to construct a product value effectiveness frontier. In order to construct an appropriate efficient frontier, a frontier type also must be selected. The constant return to scale (CRS) model is used as a default model which assume the constant growth rate. The variable returns to scale (VRS) model is preferred over the CRS since the former assumes a linear relationship between R&D spending and the number of NMEs. To measure deterioration of R&D productivity of Japanese companies from 1980 to 1997, an input VRS model was employed since there is no established approach to measure the two-stage DEA based scores. To measure the multi-dimensional R&D productivity, the input oriented VRS model is utilized to measure the cost efficiency and the output VRS model is utilized to measure the product value effectiveness of an individual company (See Table 2.1). The input oriented VRS model calculates a set of weights for every company in the data set to identify the cost efficiency index and the output oriented VRS model does the same procedure to identify the product value effectiveness index. The logic of calculating the cost efficiency index is to identify a combination of the least R&D spending of each company to produce the number of NMEs under consideration. The logic of calculating the product value effectiveness index is to identify a combination of the least number of NMEs to attain the product value under the consideration. For Japanese pharmaceutical industry, two parameters (sales and operating

profits) are employed as the product value while a single parameter, net present value, is employed as the product value for the analysis of global pharmaceutical companies.

Table 2.1. DEA models used for R&D Productivity measures

Frontier Type	Input-oriented	Output-oriented
Objective function	Min α_i	Max β_i
Constraints	Subject to $\sum_{j=1}^n \lambda_j x_j \leq \alpha_i x_i$ $\sum_{j=1}^n \lambda_j y_j \geq \alpha_i y_i$ $\sum_{j=1}^n \lambda_j = 1$ $\alpha_i \leq 1$ $\lambda_j \geq 0, j = 1, \dots, n$	Subject to $\sum_{j=1}^n \lambda_j y_j \geq \beta_i y_i$ $\sum_{j=1}^n \lambda_j z_{j1} \leq \beta_i z_{i1}$ $\sum_{j=1}^n \lambda_j z_{j2} \leq \beta_i z_{i2}$ $\sum_{j=1}^n \lambda_j = 1$ $\beta_i \geq 1$ $\lambda_j \geq 0, j = 1, \dots, n$
Definition	α_i is the cost efficiency index of i th company λ_j is a weight of the j th company when calculating α_i n is the number of selected companies x_j is accumulated R&D spending of the j th company	β_i is the product value effectiveness index of i th company λ_j is a weight of the j th company when calculating β_i n is the number of selected companies y_j is the number of NMEs of the j th company z_{j1} is the 1 st component of

	y_j is the number of NMEs of the j th company	accumulated product value of the j th company (i.e., sales for Japanese companies and net present value for global companies) z_{j2} is the 2nd component of accumulated product value of the j th company (i.e., operating profit for Japanese companies)
--	---	---

Source: modified from Caves W., Christensen R., Diewart E. [3]

2.3. Malmquist index

The Malmquist index is employed since a historical trend of DEA scores of R&D productivity does not reveal the causes of changes. The index is originally developed by Malmquist [44], and Caves et al [46] modified as the productivity index. Fare and Lovell [47] further develop the index as the DEA based Malmquist index. The Malmquist index is a method to compare productivity from one period to another and requires four steps. First, the efficient frontier in time period 1 (time t) is constructed and R&D productivity for each company is measured. Second, the efficient frontier in time period 2 (time $t+1$) is constructed and R&D productivity for each company is measured. Third, the DEA scores of time period 1 to efficient frontier at time period 2 are compared. Four, the DEA scores of time period 2 to efficient frontier at time period 1 are compared. A mathematical

formula is presented in Figure 2.3. The Malmquist index score (MI score) is a geometric mean of scores of these four components and is the productivity change between two time periods. MI score was 1 if there was no change in R&D productivity, less than 1 if there was any improvement in R&D productivity, and greater than 1 if there was any deterioration in R&D productivity.

Figure 2.3. Malmquist index Formula

$$MI\ score = \sqrt{\frac{\theta_t(x_t, y_t)}{\theta_t(x_{t+1}, y_{t+1})} \frac{\theta_{t+1}(x_t, y_t)}{\theta_{t+1}(x_{t+1}, y_{t+1})}}$$

where

MI score is the efficiency change between period t and period t+1.

$\theta_t(x_t, y_t)$ is the efficiency scores of R&D productivity at period t comparing with the frontier in time t,

$\theta_t(x_{t+1}, y_{t+1})$ is the efficiency scores of R&D productivity at period t+1 comparing with the frontier in time t+1,

$\theta_{t+1}(x_t, y_t)$ is the efficiency scores of R&D productivity at period t+1 comparing with the frontier in time t,

$\theta_{t+1}(x_{t+1}, y_{t+1})$ is the efficiency scores of R&D productivity at period t comparing with the frontier in time t+1

Source: modified from Fare R., Lovell C. [47]

The MI score can be decomposed into two mutually exclusive scores: the efficiency change (EC) and frontier shift (FS) scores. The mathematical equation is provided on Figure 2.4.

The EC score measures changes in how companies catch up to the industry

benchmark from one period to another. The FS score measures changes in the efficient frontier, which is an industry-based R&D productivity benchmark in a given year. If R&D productivity deteriorates, both scores are greater than 1.

Figure 2.4. Components of Malmquist Index formula

$$MI\ score = \frac{\theta_t(x_t, y_t)}{\theta_t(x_{t+1}, y_{t+1})} \sqrt{\frac{\theta_{t+1}(x_{t+1}, y_{t+1})}{\theta_t(x_{t+1}, y_{t+1})} \frac{\theta_{t+1}(x_t, y_t)}{\theta_t(x_t, y_t)}}$$

[Frontier shift] [Efficiency change]

where

MI score is the efficiency change between period t and period t+1.

$\theta_t(x_t, y_t)$ is the efficiency scores of R&D productivity at period t comparing with the frontier in time t,

$\theta_t(x_{t+1}, y_{t+1})$ is the efficiency scores of R&D productivity at period t+1 comparing with the frontier in time t+1,

$\theta_{t+1}(x_t, y_t)$ is the efficiency scores of R&D productivity at period t+1 comparing with the frontier in time t,

$\theta_{t+1}(x_{t+1}, y_{t+1})$ is the efficiency scores of R&D productivity at period t comparing with the frontier in time t+1

Source: modified from Fare R., Lovell C. [47]

2.4. Two-Stage DEA

There are at least four approaches to measure relative R&D productivity of the pharmaceutical industry on an individual company basis utilizing the DEA: 1) a conventional single DEA model (VRS input model), 2) a separate model, 3) a Kao-Hwang model [48], and 4) a Chen-Zhu model [40]. Although the first conventional single stage model cannot be an appropriate method,

DEA score will be shown in order to see difference between four models. Table 2.2 summarizes four potential models of R&D productivity measures. Note that under the separate model, a researcher makes qualitative judgments about outcome weights if two outcomes related to respective DEAs are simply combined. The two-stage DEA model, however, overcomes this issue by incorporating the two DEA seamlessly. Further, the two-stage DEA model illustrates the nature of the cost efficiency and its importance for a company's overall performance [40]. Since there is no constant linear relationship between R&D spending and the number of NMEs, the Kao-Hwang model, which is based on the linear relationship between them, may not be appropriate for the purpose.

Table 2.2. Comparison of four models for R&D productivity measures using DEA

	Single stage	Separate	Kao-Hwang	Chen-Zhu
DEA Model	Single-stage	Two-single stage	Two-stage	Two-stage
Efficiency Frontier type	VRS	VRS	CRS	VRS
Intermediary	None	Actual number of NMEs	Optimized number of NMEs	Optimized number of NMEs

Among three DEA models, the separate model uses two single stage DEA models while other two models are based on the two-stage DEA. Even though the name of the two-stage DEA model suggests two different

processes can be involved, two efficient measures are calculated simultaneously. There are at least two differences: objective function(s) utilized and use of intermediary (a link between the first stage and second stage). The separate model requires two separate steps to measure the overall R&D productivity. Both the Kao-Hwang and the Chen-Zhu models optimize the overall R&D productivity by subtracting a product value effectiveness index from the cost efficiency index for each company. Thus, both models guarantee an overall efficient two-stage when each stage is efficient.

The separate model does not use an intermediary while both the Kao-Hwang model and the Chen-Zhu model utilize. It is noteworthy that a managerial decision on R&D productivity enhancement plan utilizing the separate model may not achieve the overall R&D productivity [40-41]. To overcome this weakness, the intermediary, the optimized number of NMEs, plays an important role to visualize the R&D productivity issue clearly. This optimized number, however, is not necessarily equal to the actual number of NMEs if a company is not.

Figure 2.5 illustrates the R&D productivity model used in this dissertation which is based on the Chen-Zhu model. The objective function is to minimize the difference between the cost efficiency index (α in Table 2.3) and product value effectiveness index (β in Table 2.3) for every company.

Thus, the first stage measures the indirect impact of cost efficiency of the R&D productivity where the first stage uses inputs for every company and output \emptyset (the optimized number of NMEs). The value of \emptyset , output of the first stage, is also used as input in the second stage to produce outputs y (the product value). Note that \emptyset is the unknown decision variable for each company. The calculation for each company is as follows: the cost efficiency is calculated to minimize the R&D spending given the optimized number of NMEs. Second, using the optimized number, the product effectiveness is then calculated to maximize the product value. Since both the R&D spending and product value(s) must be feasible under the current conditions, iterations continue until the optimized number of NMEs matches both optimization conditions. Since the number of parameters used under the R&D productivity model is flexible, there are two product values, sales and operating profit, for the Japanese pharmaceutical industry's analysis and one product value, net present value, for the global pharmaceutical industry's analysis.

Figure 2.5. R&D Productivity Model

Objective function	Min $\alpha_i - \beta_i$
Constraints	<p>Subject to</p> $\sum_{j=1}^n \lambda_j x_j \leq \alpha_i x_i$ $\sum_{j=1}^n \lambda_j y_j \geq \Phi_i$ $\sum_{j=1}^n \mu_j y_j \leq \Phi_i$ $\sum_{j=1}^n \mu_j z_{j1} \geq \beta_i z_{i1}$ $\sum_{j=1}^n \mu_j z_{j2} \geq \beta_i z_{i2}$ $\sum_{j=1}^n \lambda_j = 1, \quad \sum_{j=1}^n \mu_j = 1$ $\alpha_i \leq 1, \quad \beta_i \geq 1$ $\lambda_j, \mu_j \geq 0, j = 1, \dots, n$
Definition	<p>α_i is the cost efficiency index of ith company β_i is the product value effectiveness index of ith company λ_j is a weight of the jth company for α_i μ_j is a weight of the jth company for β_i n is the number of selected companies x_j is accumulated R&D spending of the jth company y_j is the number of NMEs of the jth company z_{j1} is the 1st component of accumulated product value of the jth company z_{j2} is the 2nd component of accumulated product value of the jth company</p>

Source: modified Chen Y., Zhu J. [4]

The Cost efficiency and the Product value indices for every company are calculated with the following algorithm (Figure 2.6).

Figure 2.6. R&D Productivity Model algorithm

Step 1: Calculation of the cost efficiency index

Identify the number of optimized NMEs of the *i*th company and calculate the cost efficiency index of *i*th company by identifying a set of weight for all companies in the universe with the accumulated R&D spending, and the number of NMEs.

Step 2: Calculation of the product value effectiveness index

Calculate the product value effectiveness index by identifying a set of weights for all companies in the universe with the optimized number of NMEs from the Step 1 and the product value(s) of the *i*th company. In this step, verify the product value of the optimized number of NMEs should not exceed the product value of the actual number of NMEs. If the product value of the optimized number of NMEs exceeds the product value of the actual number of NMEs, recalculate the new optimized number of NMEs, and go to Step 1 to recalculate the cost efficiency index.

Step 3: Criteria check

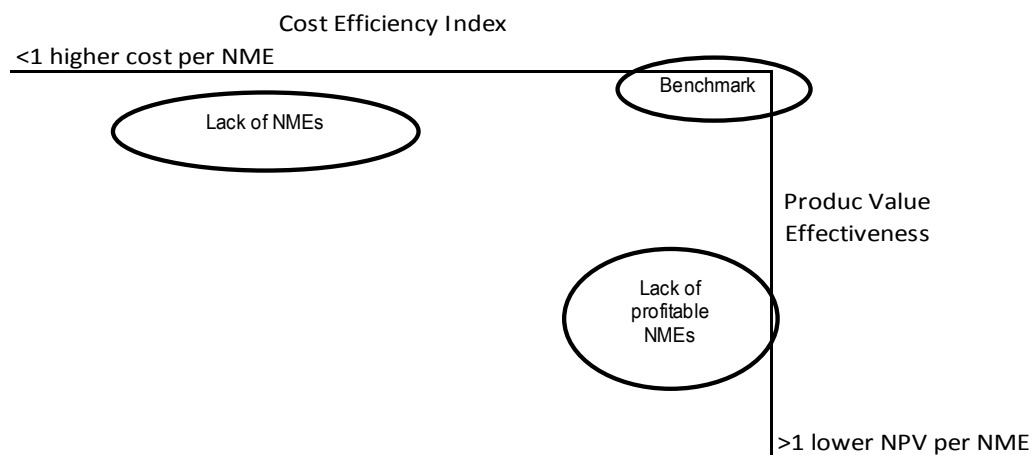
Calculate the difference of two indices from Step 1 and 2. If the difference is the lowest number possible, stop the iteration and continue Step1 to Step 3 for the rest of companies. If the difference can be further minimized, go to Step 1 to recalculate the cost efficiency and product value effectiveness indices.

2.5. R&D productivity map (RDP map)

The construction of an RDP map consists of two steps. First, cost efficiency index and product value effectiveness index for each company are calculated

using the R&D productivity model. Second, these scores are then plotted on a map. A schematic view of the RDP map is shown in Figure 2.7. The cost efficiency index, the vertical axis on the map, approaches from 0 to 1 as the company produces an NME at the lowest cost possible relative to the benchmark. The product value effectiveness index, the horizontal axis, approaches to infinity to 1 as the company becomes the highest aggregated NPV per total number of NMEs relative to the benchmark. In this way, higher DEA scores for product value effectiveness indicate a lower degree of product value effectiveness. More shifts to the left of the origin, less efficient in developing NMEs a company is, indicating a company's relying on a few profitable drugs lower shift of the origin, less effective in NPV of NMEs the company is, indicating that their current pipeline net present value (NPV) does not carry the high NPV.

Figure 2.7. Schematic view on the RDP map



After mapping DEA scores, companies can be classified into four groups. The first group represents a benchmark company that located on the origin of the map, indicating its optimal cost efficiency and effectiveness. Companies in the second group are located to the upper left of the origin, indicating that the companies' NPVs may rely on a relatively small number of NMEs. To increase R&D productivity, companies in this group should consider licensing, product alliances, and M&A. Companies that fall below the origin constitute the third group. Although companies in the third group are cost-efficient, they are not successful in terms of product value effectiveness. It would behoove companies in this group to review the value of each NME and justify a continuation of clinical trials. Companies that are distant from the origin comprise the fourth group. This group is characterized by R&D productivity values that may not enhance their corporate value. While other alternatives can be considered, the map penalizes the company if the alternative to enrich the pipeline with little product value added. The company should balance both cost efficiency and product value effectiveness to enhance the pipeline value and reduce the product risk at the same time.

To clarify advantages using the RDP map, the objectives of the separate and RDP maps should be explained. The objective of the input oriented model, or calculation of the cost efficiency index of the separate model, is to reduce the

R&D spending to produce the same number of NMEs while the objective of the output oriented model, or calculation of the product value effectiveness of the separate model, is to maximize the product value employing the current number of NMEs. Given this, the separate model projects the current status of the industry of the two aspects of the R&D productivity separately. This may cause an additional issue of unbalancing trade-offs between the cost efficiency and product value effectiveness. Since the objective of the RDP map is to minimize the difference between the cost efficiency and the product value effectiveness indices, results from this model projects levels of inefficiency to attain the balanced R&D productivity. The difference between the separate and RDP maps will be discussed in Chapter 4.

2.6. Data descriptions

While the R&D productivity model requires input, intermediary, and output variables, analysis on Japan and global industry utilizes the different variables. Table 2.3 compares variables used for both cases.

Table 2.3. List of variables used for Japanese and global pharmaceutical industries

		Japanese companies	Global companies
Input	R&D Spending	8 year accumulated 3 years moving average R&D spending	5 year accumulated R&D spending
Output	Number of NMEs	Weighted number of approved NMEs	Actual number of NMEs marketed, filed, or in Phase III trials
Outcome	Product Value	Sales and Operating Profit	Net Present Value

2.6.1. Data description on Japanese pharmaceutical industry

In the analysis on Japanese pharmaceutical industry, 24 companies are originally selected but a final sample of 15 companies is obtained after applying the following exclusion criteria: 1) availability of financial data and 2) significant change in management control. One input and three output variables are selected to measure changes in R&D productivity from 1980 to 1997: the actual R&D spending as the sole input, and the accumulated number of weighted NMEs approved by the MHLW, sales, and operating profit as the three output variables. For the R&D productivity model, the same variables are utilized but the accumulated number of weighted NMEs will be used as the intermediary variable, instead of output variable. Table 2.4 illustrates the historical change in sales, operating profit

and R&D spending of the industry.

Table 2.4. Financial data and the number of NMEs approved from 1980 to 1997

	R&D/Sales	Gross Profit/Sales	Sales Expenses/Sales	Operating Profit/Sales	# of NMEs
1980	3.26%	53.02%	18.44%	12.45%	12
1981	3.50%	53.01%	18.88%	11.86%	29
1982	3.69%	53.10%	18.71%	11.68%	15
1983	4.14%	53.92%	19.01%	10.30%	15
1984	4.71%	54.31%	19.41%	8.91%	7
1985	5.28%	52.97%	19.93%	9.11%	20
1986	5.56%	51.06%	19.75%	10.79%	7
1987	5.74%	49.18%	19.64%	12.45%	20
1988	5.87%	48.86%	19.73%	12.55%	10
1989	6.23%	48.06%	20.71%	11.54%	14
1990	6.80%	47.34%	21.69%	10.41%	8
1991	7.17%	46.88%	21.86%	10.35%	12
1992	7.45%	45.78%	21.12%	12.07%	9
1993	8.06%	44.79%	21.20%	12.80%	22
1994	8.49%	44.31%	20.43%	13.54%	10
1995	8.89%	43.10%	20.88%	13.84%	9
1996	9.22%	42.75%	20.08%	15.28%	4
1997	9.84%	42.04%	19.35%	15.52%	5

Source: company annual reports

The R&D spending of a particular year is averaged over three years to consider accounting time delay of R&D spending. The time lag between the R&D spending and its outcome is assumed as eight years [49-50]. The “Annual Statistical Survey on Trends in Pharmaceutical Production” published by the MHLW is employed to determine the number of NMEs. An interview form provided by the company that seeks approval from the MHLW was employed to identify the originator of the NMEs for each NME under consideration. To distinguish between internal and licensed NMEs, cost allocation among the clinical phases was considered. The average expected cost of the clinical period was 60.6 million dollars in 2000, and the

expected cost in Phase III was 27.1 million dollars or 44.7% of the total clinical cost [4]. There are two basic methods for a company to receive approval from the MHLW: 1) registering as an original drug developer and 2) registering as a co-development partner. Because there is little information on the clinical stage of the licensed NMEs, the weight for a licensed-in NME is set as 50% and a co-development NME is set as 20% of the R&D spending prior to the NME's approval. It is possible to identify these since MHLW classifies drugs by efficacy into 34 classes and 177 subclasses. Pharmaceutical companies must complete and submit an interview form to the MHLW, disclosing detailed information on their approved drugs such as the origin of NMEs, in order for those drugs to be listed under the MHLW's reimbursement list.

Table 2.5 illustrates the percentage of major therapeutic categories and breakdown of antibiotics, the largest drug production amount in Japan from 1973 to 1988. The total antibiotics productions represent 24.2% of the total production in 1976 and lasts its largest share of production amounts until 1989. There are 9 subclasses for antibiotics. For example, the code number 613 is for antibiotic preparations acting mainly on gram-positive, gram-negative bacteria and antibiotics, mainly cepham antibiotics. The code number 624 is for synthetic antibacterial and they are mainly new quinolone antibiotics. There were 9 antibiotics approved under the code

number 624 which was introduced in 1991. Prior 1991, synthetic antibacterial were approved but no data were available. Among antibiotics production, the production amount of the code number 613 represented 16.5% in 1976 or was bigger than the production amount of the digestive system drugs until 1991. In this study, the relationships between R&D productivity and therapeutic categories are verified. Antibiotics, central nervous system (CNS), digestive system, and various cardiovascular and metabolism franchises life style disease drugs are chosen.

Table 2.5. Japanese pharmaceutical drug production amount from 1976 to 1997 and its production share by therapeutic categories

Year	Total (billion JPY)	Antibiotics					Life style related diseases			CNS	Digestive System	Others
		Subtotal	('613)	('624)	('others)	Subtotal	Cardiovascular	Other Metabolism				
1976	2,162	24.2%	16.5%	0.0%	7.6%	19.9%	9.0%	10.9%	10.7%	7.5%	37.7%	
1977	2,458	23.8%	16.8%	0.0%	6.9%	20.4%	9.8%	10.6%	10.5%	7.6%	37.7%	
1978	2,794	22.8%	16.9%	0.0%	5.9%	20.6%	9.9%	10.7%	10.3%	7.6%	38.7%	
1979	3,042	21.6%	16.3%	0.0%	5.3%	20.5%	10.2%	10.4%	10.0%	7.9%	39.9%	
1980	3,482	23.4%	18.2%	0.0%	5.1%	21.3%	10.8%	10.5%	9.9%	7.4%	38.1%	
1981	3,679	21.2%	16.8%	0.0%	4.4%	21.9%	11.9%	10.0%	9.6%	7.7%	39.6%	
1982	3,980	21.7%	18.0%	0.0%	3.8%	20.4%	11.1%	9.3%	9.7%	8.1%	40.1%	
1983	4,032	18.3%	14.3%	0.0%	4.0%	21.6%	12.6%	9.0%	9.8%	8.4%	41.9%	
1984	4,027	19.5%	16.1%	0.0%	3.4%	21.4%	13.2%	8.2%	9.8%	8.5%	40.7%	
1985	4,002	18.2%	15.1%	0.0%	3.1%	20.8%	13.0%	7.8%	9.6%	8.8%	42.5%	
1986	4,281	16.7%	14.0%	0.0%	2.7%	20.8%	13.2%	7.7%	10.1%	8.7%	43.7%	
1987	4,825	15.9%	13.5%	0.0%	2.4%	21.1%	13.4%	7.6%	10.3%	9.1%	43.7%	
1988	5,059	14.7%	12.5%	0.0%	2.2%	21.6%	13.8%	7.8%	10.2%	9.1%	44.4%	
1989	5,502	14.0%	12.0%	0.0%	1.9%	21.9%	14.0%	7.9%	10.2%	9.5%	44.5%	
1990	5,595	11.8%	10.1%	0.0%	1.8%	23.1%	14.8%	8.3%	9.8%	9.3%	45.9%	
1991	5,697	12.9%	9.1%	2.0%	1.9%	23.7%	15.5%	8.2%	10.0%	9.3%	44.0%	
1992	5,574	10.5%	6.7%	1.7%	2.0%	24.2%	15.1%	9.1%	9.1%	7.9%	48.3%	
1993	5,695	10.8%	6.7%	2.1%	2.0%	24.7%	15.5%	9.2%	9.7%	8.8%	46.0%	
1994	5,750	9.1%	5.7%	1.7%	1.7%	26.0%	16.4%	9.6%	9.8%	9.1%	45.9%	
1995	6,168	10.1%	6.2%	2.0%	1.8%	26.0%	16.4%	9.6%	9.4%	8.9%	45.6%	
1996	6,100	8.7%	5.4%	1.8%	1.6%	26.4%	16.6%	9.8%	9.2%	9.1%	46.6%	
1997	6,148	9.0%	5.8%	1.5%	1.8%	26.2%	16.6%	9.5%	9.4%	9.3%	46.2%	

Source: modified data from the Minister of Health, Labor, and Welfare [51]

Table 2.6 illustrates that ethical drugs approved by major therapeutic categories from 1980 to 1997. Appendix A lists all drugs approved by MHLW from 1980 to 1997. From 1980 to 1989, 410 NMEs were approved and 56 were antibiotics. From 1990 to 1999, 238 NMEs were approved and 17 were antibiotics. Among 76 antibiotics approved from 1980 to 1999, 47 antibiotics (24 were Japan origin) were approved under the code number 613.

Table 2.6. Trends of Japanese ethical drug approved by franchise category from 1980 to 1997

Year	Antibiotics				CNS	Digestive System	Life Style Diseases	Total
	Subtotal	(613)	(624)	Others				
1980	5	4		1	5			33
1981	13	8		5	3	4	5	58
1982	3	2		1	1	2	5	35
1983	4	3	1	0	4	2	5	42
1984	1	1		0		3	3	24
1985	8	3	2	3	2	2	2	56
1986	8	6		2			1	42
1987	10	7	1	2		4	2	55
1988				0	3	2	5	39
1989	5	3	2	0	1		4	26
1990	3			3	2	2	3	29
1991	1	1		0			4	36
1992	2	1		1		1	3	25
1993	5	2	3	0		1	4	47
1994	1	1		0		1	6	43
1995	3	3		0			5	21
1996				0				21
1997	2	2		0		1	2	16

Source: modified data from the Minister of Health, Labor, and Welfare [52]

Table 2.7 illustrates the number of NMEs of 15 Japanese companies by therapeutic categories from 1980 to 1997. There were 239 NMEs approved

by the MHLW out of 648 NMEs approved by the MHLW. Shionogi received 29 approvals followed by Daiichi and Takeda. Among 648 NMEs, 74 were antibiotics and followed by life style disease of 60.

Table 2.7. List of domestic approved NMEs by company

	Antibiotics	Life style diseases	Digestive systems	CNS	Cardiovascular	Respiratory	Others	Total
Chugai		1					5	6
Daiichi	2	3		2	2		22	27
Dainippon	2	2					9	13
Eisai		2	2	1			11	15
Fujisawa	3	2	1	1			10	16
Kaken	1			1		1	10	11
Ono							7	7
Sankyo	3	7	1	3		1	11	22
Shionogi	9	3	2		1		15	29
Takeda	7	3	1	1			14	25
Tanabe	1	1	2				10	14
Tokyo Tanabe						1	7	7
Toyama chemical	3	1	1				3	8
Yamanouchi	3	3	1	1	1		17	24
Yoshitomo	3	2	2	1			8	15
Subtotal	37	30	13	11	4	3	159	239
Foreign	14	11	4	3	2	2	129	158
Others	23	19	8	7	6	5	201	251
Total	74	60	25	21	12	10	489	648

Source: company annual reports and interview forms.

Furthermore, relationships between four largest therapeutic categories including antibiotics subclasses of 613 and 624 and deterioration of R&D productivity using the Malmquist Index are also investigated. Table 2.8 lists antibiotics strategy such as in-house development or licensing and subclass development by company.

Table 2.8. Therapeutic development strategy by company from 1980 to 1997

Company Name	Sales in JPY billion	Antibiotics development			Lifestyle disease drug development	Digestive drug development
		Internally developed (I), Licensed (L), or None (N)	Internally Developed between 1980 and 1997	Focus on subclass	Internally developed (I), Licensed (L), or None (N)	Internally developed (I), Licensed (L), or None (N)
Chugai	> 50	N	N	No development	I	L
Daiichi	> 50	I	Y	624	I	L
Dainippon	> 50	I	Y	624	I	L
Eisai	> 100	N	N	No development	I	I
Fujisawa	> 100	I	Y	613	I	L
Kaken	< 50	L	Y	613	N	N
Nippon Shinyaku	< 50	N	N	No development	N	I
Sankyo	> 100	I	Y	both '613 and '624	I	I
Shionogi	> 100	I	Y	both '613 and '624	L	L
Takeda	> 100	I	Y	613	I	I
Tanabe	> 100	I	Y	613	N	L
Tokyo Tanabe	< 50	N	N	No development	N	N
Toyama Chemical	< 50	I	Y	both '613 and '624	L	I
Yamanouchi	> 50	I	Y	613	I	I
Yoshitomi	< 50	L	N	613	I	L

Source: company annual reports and interview forms.

Table 2.9, Table 2.10, and Table 2.11 summarize data used for analysis in 1997, 2003, and 2006, respectively. Figures for Daiichi Sankyo and Astellas in 2006 are simply added two companies' results, respectively.

Table 2.9. Accumulated R&D spending, actual and adjusted number of NMEs, accumulated sales, and accumulated operating profits for Japanese companies from 1980 to 1997

(unit; million yen except NMEs)	R&D spending	Actual number of NMEs	Adjusted number of NMEs	Sales	Operating Profit
Tokyo Tanabe	23,994	9	5.2	252,030	35,865
Toyama Chemical	26,100	9	7.0	251,392	36,292
Kaken	26,194	11	6.9	272,135	35,226
Nippon Shinyaku	27,031	7	4.5	256,817	35,679
Yoshitomi	30,618	15	10.4	317,786	44,381
Dainippon	31,030	15	9.7	346,211	38,888
Tanabe	40,296	14	10.5	390,592	48,536
Chugai	42,505	6	4.5	372,718	49,478
Daiichi	43,469	26	18.2	441,181	74,505
Shionogi	46,037	29	18.2	420,295	47,743
Fujisawa	48,781	18	12.5	423,778	52,152
Yamanouchi	49,126	26	18.7	526,396	99,555
Eisai	50,991	15	11.0	467,271	78,091
Sankyo	54,102	22	14.9	671,167	158,382
Takeda	75,288	25	23.0	848,710	136,630

Table 2.10. Accumulated R&D spending, actual and adjusted number of NMEs, accumulated sales, and accumulated operating profits for Japanese companies from 1980 to 2003

(unit; million yen except NMEs)	R&D spending	Actual number of NMEs	Adjusted number of NMEs	Sales	Operating Profit
Kaken	96,276	12	7.7	72,706	7,526
Nihon Shinyaku	117,201	8	3.3	51,326	3,477
Dainippon	177,200	16	9.6	170,842	9,283
Tanabe	322,376	19	13.4	173,613	29,440
Daiichi	375,113	29	19.7	322,767	46,114
Shionogi	437,112	29	17.7	200,485	20,292
Yamanouchi	461,818	31	22.4	511,208	105,698
Eisai	506,108	17	13	500,164	83,061
Fujisawa	507,199	21	15.2	395,401	56,703
Sankyo	578,375	25	17.5	596,345	95,555
Takeda	954,699	31	26.7	1,086,431	371,633

Table 2.11. Accumulated R&D spending, actual and adjusted number of NMEs, accumulated sales, and accumulated operating profits for Japanese companies from 1980 to 2006

(unit; million yen except NMEs)	R&D spending	Actual number of NMEs	Adjusted number of NMEs	Sales	Operating Profit
Kaken	113,431	13	7.7	76,415	8,113
Nihon Shinyaku	147,175	8	3.3	56,320	5,220
Tanabe	386,381	20	14.2	177,531	30,456
Shionogi	521,600	32	18.9	199,759	28,863
Eisai	660,122	17	13.0	674,111	105,263
Takeda	1,236,419	33	26.9	1,305,167	458,500
Astellas	1,276,551	53	38.9	972,586	275,904
DaiichiSankyo	1,289,268	57	39.2	880,120	156,827

1980 is selected as the start of the study period because this was when the MHLW started the current approval system. There are also at least three reasons to select 1997 as an observation year for the first case. The first reason is that Japanese companies had developed several key drugs approved between 1980 and 1997, which are still available in 2012 and sold with significant amounts even after the patent expiry (See Table 2.12).

Table 2.12. List of ethical drugs developed from 1980 to 1999 with sales above 30 billion yen in 2010

Year of Domestic approval	Company	Generic name	Category	Sales in FY2010 (billion yen)
1978	Eisai	Mecobalamin	Vitamin B12	30.4
1985	Yamanouchi	famotidine	Digestive drug	41.7
1986	Sankyo	Loxoprofen Sodium Hydrate	Inflammatory drug	54.2
1987	Seikagaku/Kaken	Sodium hyaluronate	Joint dysfunction drug	30.8
1988	Otsuka	Cilostazol	Antiplatelet drug	46.5
1988	Ono	Limaprost alfadex	Hormone	40.1
1998	Hisamitsu	Ketoprofen	Inflammatory patch	86.4
1989	Sankyo	pravastatin sodium	Cholesterol lowering drug	38.1
1990	Chugai	Epoetin Beta	Anemia	40.0
1990	Mochida	Ethyl icosapentate	Cholesterol lowering drug	37.0
1992	Takeda	lansoprazole	Digestive drug	70.9
1992	Takeda	Leuprorelin Acetate	Cancer drug	65.9
1993	Fujisawa	Tacrolimus	immunosuppressive drug	39.6
1993	Daiichi	levofloxacin	Antibiotics	32.4
1994	Takeda	Voglibose	Diabetics drug	32.2
1995	Ono	Pranlukast Hydrate	Asthma	30.0
1997	Eisai	Rabeprazole	Digestive drug	60.2
1999	Takeda	Candesartan	Hypertension drug	122.9
1999	Takeda	Pioglitazone hydrochloride	Diabetics drug	122.9
1999	Eisai	Donepezil	Digestive drug	93.6
1999	Taiho	Tegafur	Anticancer drug	37.1

Source: company annual reports.

The second reason is that the first industry consolidation was occurred in 1998. Prior to the first merger between two mid-size, public Japanese pharmaceutical companies, namely Green Cross and Yoshitomi, there was no major industry consolidation has occurred. Two months after this merger, Japan Tobacco acquired the majority share of Torii Pharmaceutical and expanded into the drug development and marketing in Japan. In 1999, Mitsubishi Chemical, the largest chemical company in Japan, acquired

Tokyo Tanabe, a small-size pharmaceutical company. Table 2.13 shows the industry consolidation events of the Japanese pharmaceutical industry from 1998 to 2012. The first wave of industry consolidation was observed between 1998 and 2001 and the second wave was observed between 2005 and 2007. The third wave has led to acquire overseas companies in order to gain global business platforms and/or expanding its therapeutic franchise such as cancer. It is interesting to note that companies merged in the first wave of industry consolidation were mainly companies with the revenue of less than 50 million yen. The third reason is that the R&D deterioration was observed in late 1990s as mentioned in the previous chapter [51]. There were 14 industry consolidation events between 1980 and 2005, and our selected companies involved in 9 events.

Table 2.13. Industry consolidations of the Japanese pharmaceutical industry

Year	Events	Companies
1982	Minority share acquisition	Merck Banyu
1998	Meger (Domestic)	Yoshitomi Green Cross
1998	Majority share acquisition	Japan Tobacco Torii Pharmaceutical
1999	Meger (Domestic)	Mitsubishi Chemical Tokyo Tanabe
2000	Meger	Schering Mitsui Pharmaceutical
2000	Majority share acquisition	Boehringer Ingelheim SS Pharmaceutical
2001	Meger (Domestic)	Mitsubishi Chemical Yoshitomi
2001	Majority share acquisition	Roche Chugai
2002	Majority share acquisition	Taisho Pharmaceutical Toyama Chemical
2003	Merger	Merck Banyu
2003	Merger	Abbott Hokuriku
2005	Meger	Takeda Syrx
2005	Meger (Domestic)	Yamanouchi Fujisawa
2005	Meger (Domestic)	Sumitomo Chemical Daiippon
2007	Meger (Domestic)	Daichi Sankyo
2007	Meger (Domestic)	Mitsubishi Chemical Tanabe
2007	Meger	Eisai Morphotek
2007	Meger	Astellas Agensys
2008	Meger	Daichi Sankyo U3 Pharma
2008	Meger	Eisai MGI Pharma
2008	Meger	Takeda Amgen Japan
2008	Meger	Takeda Millennium Pharmaceuticals
2008	Majority share acquisition	Daichi Sankyo Ranbaxy
2008	Meger	Shionogi Sciele Pharma
2008	Meger	Fuji Film Holdings/ Taisho Toyama Chemical
2009	Meger	Daiippon Sumitomo Sepracor
2009	Meger	Hisamitsu Noven Pharmaceuticals
2009	Meger	Eisai AkaRx
2010	Meger	Astellas OSI Pharmaceuticals
2011	Meger	Shionogi C&O Pharmaceutical Technology
2011	Meger	Kyowa Hakko Kirin ProStrakan
2011	Meger	Daichi Sankyo Plexxikon
2011	Meger	Takeda Nycomed
2011	Meger	Taisho Pharmaceutical Hoepharma

Source: company annual reports

2.6.2. Data descriptions on global pharmaceutical industry

Although the top 50 pharmaceutical companies in term of global sales in 2007 are originally considered for inclusion in this study, pharmaceutical companies that did not provide sufficient information to calculate their respective productivities are excluded. This includes companies that (a) did not disclose their R&D spending related to product development, (b) did not have any NMEs in P-III clinical trials, or (c) did not launch any NMEs during 2002 and 2007. Three variables are utilized to evaluate R&D productivity of 21 global pharmaceutical companies: (a) a company's cumulative R&D spending from 2002 to 2007 and from 2007 to 2012, (b) number of NMEs, and (c) aggregate net present value (NPV) of the company. R&D spending from 2002 to 2012 is obtained from annual reports generated by each respective company. NMEs that were launched prior to 2002 are eliminated because they would not factor into the calculation of R&D productivity between 2002 and 2007. NMEs in the dataset are included if they were engaged in a Phase III study that had been initiated between 2002 and 2007. This was motivated by a study by DiMasi [4] that reported that a P-III clinical trial required 33.8 months to perform and the median approval time for non-priority new NMEs dropped from 27 months to 14 months, five years are considered to be a reasonable time range for estimating R&D productivity [51]. NMEs entering late-stage clinical trials

are focused because such a management decision is paramount in driving productivity [52].

Data related to NPVs of 19 global pharmaceutical companies are obtained from Pharmapipeline®, which is provided by Barclays Capital. Pharmapipeline® is a data book of NPV that is prepared by industry analysts around the world. These analysts calculate each NPV on the basis of products' contributions to profits that had been launched or were in development over a full and variable product lifecycle. They also consider the timing with which products are launched in different regions. Each product is subject to initial fixed launch costs (30% of peak sales spread over the first 24 months of launch) and a progressive underlying operating margin. They do not assign R&D costs on a per-product basis since much of the R&D spending is a historical sunk cost and established pharmaceutical companies have existing cash flow to fund late-stage drug developments. Any individual drugs are modelled on a marginal profit basis.

Of the 21 companies included in our sample (see Table 2.14), nine U.S. pharmaceutical companies (i.e., Abbott, Amgen, Biogen Idec, Bristol-Meyers Squibb, E. Lilly, Merck, Pfizer, Schering Plough, and Wyeth) spent 155.7 billion dollars and produced 98 NMEs between 2002 to 2007. The cumulative NPV of these NMEs was 97 billion dollars. Six Japanese pharmaceutical companies (Astellas, Daiichi Sankyo, Eisai, Ono, Shionogi,

and Takeda) spent 36.1 billion dollars from 2002 to 2007 and produced 50 NMEs. The cumulative NPV of the Japanese NMEs during this time period was 15.5 billion dollars. Six European pharmaceutical companies (AstraZeneca, GSK, Novartis, Novo Nordisk, Roche, and Sanofi) spent 148.3 billion dollars between 2002 and 2007, and produced 126 NMEs. The total NPV of these NMEs was 110.9 billion dollars.

Table 2.14. Financial, number of NMEs and net present value by origin of the company in 2007 (unit: billion us dollars)

	R&D spending		# of NMEs		NPV		
	Amount	%	Amount	%	Amount	%	
US	Biogen	3,773	1.1%	8	2.9%	7,080	3.2%
	Schering Plough	11,480	3.4%	18	6.6%	4,657	2.1%
	Abbott	11,574	3.4%	12	4.4%	4,548	2.0%
	Amgen	13,746	4.0%	5	1.8%	15,226	6.8%
	Wyeth	15,750	4.6%	7	2.6%	4,145	1.9%
	Bristol Meyers Squib	16,092	4.7%	10	3.6%	11,137	5.0%
	E. Lilly	16,832	4.9%	6	2.2%	5,461	2.4%
	Merck	23,379	6.9%	17	6.2%	27,122	12.1%
	Pfizer	43,121	12.7%	15	5.5%	17,694	7.9%
	Sub Total	155,747	45.8%	98	35.8%	97,070	43.4%
EU	Novo	5,673	1.7%	4	1.5%	5,848	2.6%
	AstraZeneca	22,430	6.6%	13	4.7%	8,052	3.6%
	Sanofi	23,486	6.9%	29	10.6%	18,674	8.4%
	Novartis	28,906	8.5%	32	11.7%	25,185	11.3%
	Roche	33,807	9.9%	15	5.5%	14,793	6.6%
	GSK	34,063	10.0%	33	12.0%	38,435	17.2%
	Sub Total	148,365	43.6%	126	46.0%	110,987	49.6%
Japan	Shionogi	1,927	0.6%	5	1.8%	663	0.3%
	Ono	1,932	0.6%	5	1.8%	336	0.2%
	Eisai	5,298	1.6%	13	4.7%	1,322	0.6%
	Astellas	8,110	2.4%	8	2.9%	3,602	1.6%
	DaichiSankyo	8,883	2.6%	12	4.4%	2,714	1.2%
	Takeda	10,018	2.9%	7	2.6%	6,921	3.1%
	Sub Total	36,168	10.6%	50	18.2%	15,558	7.0%
Grand Total	340,281	100.0%	274	100.0%	223,615	100.0%	

Source: company annual reports and Barclays Capital.

In 2012, Wyeth and Schering-Plough are excluded but their R&D spending

is added to Pfizer and Merck, respectively. Of the 19 companies included in our sample (see Table 2.15), seven U.S. pharmaceutical companies (i.e., Abbott, Amgen, Biogen Idec, Bristol-Meyers Squibb, E. Lilly, Merck, and Pfizer) spent 172.2 billion USD and produced 57 NMEs between 2008 to 2012. The cumulative NPV of these NMEs was 44.8 billion dollars. Six Japanese pharmaceutical companies (Astellas, Daiichi Sankyo, Eisai, Ono, Shionogi, and Takeda) spent 44.6 billion dollars from 2008 to 2012 and produced 55 NMEs. The cumulative NPV of the Japanese NMEs during this time period was 18.0 billion dollars. Six European pharmaceutical companies (AstraZeneca, GSK, Novartis, Novo Nordisk, Roche, and Sanofi) spent 181.9 billion dollars between 2008 and 2012, and produced 40 NMEs. The total NPV of these NMEs was 75.3 billion dollars.

Table 2.15. Financial, number of NMEs and net present value by origin of the company in 2012(unit: billion us dollars)

	R&D spending		# of NMEs		NPV		
	Amount	%	Amount	%	Amount	%	
US	Biogen	5,748	1.4%	3	2.0%	1,710	1.2%
	Amgen	15,221	3.8%	3	2.0%	3,871	2.8%
	Abbott	15,792	4.0%	3	2.0%	1,550	1.1%
	Bristol Meyers Squib	17,919	4.5%	6	3.9%	12,647	9.2%
	E. Lilly	21,559	5.4%	9	5.9%	4,102	3.0%
	Merck	43,634	10.9%	20	13.2%	11,636	8.4%
	Pfizer	52,143	13.1%	13	8.6%	9,262	6.7%
Sub Total	172,016	43.2%	57	37.5%	44,778	32.4%	
EU	Novo	8,080	2.0%	4	2.6%	24,442	17.7%
	AstraZeneca	25,591	6.4%	4	2.6%	6,055	4.4%
	Sanofi	31,788	8.0%	8	5.3%	4,351	3.2%
	GSK	31,792	8.0%	13	8.6%	18,132	13.1%
	Novartis	39,769	10.0%	6	3.9%	14,748	10.7%
	Roche	44,916	11.3%	5	3.3%	7,520	5.4%
Sub Total	181,936	45.6%	40	26.3%	75,248	54.5%	
Japan	Ono	2,050	0.5%	3	2.0%	410	0.3%
	Shionogi	2,502	0.6%	4	2.6%	549	0.4%
	Eisai	7,456	1.9%	11	7.2%	5,389	3.9%
	Astellas	8,990	2.3%	9	5.9%	2,983	2.2%
	DaïichiSankyo	9,270	2.3%	10	6.6%	2,062	1.5%
	Takeda	14,404	3.6%	18	11.8%	6,648	4.8%
Sub Total	44,672	11.2%	55	36.2%	18,041	13.1%	
Grand Total	398,624	100.0%	152	100.0%	138,067	100.0%	

Source: company annual reports and Barclays Capital.

Table 2.16 shows that the cancer R&D franchise had the largest NPV, followed by vaccines. Appendix 2 provides a full list of the NMEs launched, filed and in Phase III trials according to therapeutic categories in 2007.

Table 2.16. Comparison of NMEs by company and therapeutic category in 2007

(Unit US million dollars)	Cancer	Cardiovascular	CNS	Diabetes	Vaccine	Others	Total
Ono	0	0	69	162	0	105	336
Shionogi	0	208	39	0	0	416	663
Eisai	291	0	245	143	0	643	1,322
DaiichiSankyo	0	1,432	54	991	0	237	2,714
Astellas	0	973	0	0	0	2,629	3,602
Wyeth	0	0	1,646	0	104	2,395	4,145
Abbott	0	1,917	0	0	128	2,503	4,548
Schering Plough	489	849	1,332	0	0	1,987	4,657
E. Lilly	236	2,630	0	2,179	0	416	5,461
Novo	0	0	0	5,275	0	573	5,848
Takeda	0	1,724	1,082	1,970	0	2,145	6,921
Biogen	652	0	5,952	0	0	476	7,080
AstraZeneca	3,030	1,330	1,252	475	1,737	228	8,052
BMS	5,435	750	0	963	0	3,989	11,137
Roche	5,264	12	117	0	0	9,400	14,793
Amgen	9,478	0	0	0	0	5,748	15,226
Pfizer	9,988	830	114	0	0	6,762	17,694
Sanofi	3,744	3,799	2,970	1,026	3,184	3,951	18,674
Novartis	4,667	6,483	349	3,173	1,945	8,568	25,185
Merck	314	3,467	975	11,046	8,527	2,793	27,122
GSK	12,664	325	2,928	270	18,207	4,041	38,435

Source: company annual reports and Barclays Capital.

Table 2.17 illustrates that in 2012, the cancer R&D franchise also had the largest NPV, followed by Central Nervous System (CNS). Appendix 3 provides a full list of the NMEs launched, filed and in Phase III trials according to therapeutic categories in 2012. To identify a relationship between the R&D productivity and therapeutic category, five largest therapeutic categories: cancer, vaccine, diabetes, cardiovascular, and CNS for 2007 and cancer, diabetes, cardiovascular, CNS, and respiratory in 2012 are selected.

Table 2.17. Comparison of NMEs by company and therapeutic category in 2012

	Cancer	Cardiovascular	CNS	Diabetes	Respiratory	Others	Total	
Abbott	700	0	0	0	0	0	850	1,550
Amgen	1,707	0	0	0	0	0	2,164	3,871
Astellas	273	0	0	0	83	873	1,755	2,983
AstraZeneca	542	5,271	64	0	0	0	178	6,055
Biogen	274	0	1,272	0	0	0	164	1,710
BMS	4,428	3,436	0	131	0	0	4,652	12,647
DaiichiSankyo	459	418	195	0	0	0	990	2,062
Eisai	3,011	0	1,068	228	0	0	1,082	5,389
E. Lilly	543	0	2,391	1,168	0	0	0	4,102
GSK	1,342	1,564	718	371	11,810	0	2,326	18,132
Merck	634	3,705	749	901	279	0	5,368	11,636
Novartis	1,742	0	12,416	0	590	0	0	14,748
Novo	0	0	0	24,293	0	0	148	24,442
Ono	0	0	320	90	0	0	0	410
Pfizer	2,594	2,847	440	0	0	0	3,381	9,262
Roche	3,069	0	0	0	0	0	4,452	7,520
Sanofi	1,433	1,501	950	471	0	0	0	4,351
Shionogi	0	48	238	0	0	0	263	549
Takeda	467	912	1,259	2,179	0	0	1,832	6,648

Source: company annual reports and Barclays Capital.

Further, 2007 is selected as the endpoint of the time during which data were collected because it marked a period just before a large number of M&A activities occurred. There had been no major M&A events since 2002, and the interest is to evaluate how R&D productivity between 2002 and 2007 affected the industry subsequently. There is a possibility that M&A activities may skew R&D spending if any reviews were made following the M&A event. 2012 is also selected as the endpoint of the time period due to its data availability. The respective values of the M&A in which our sample companies engaged are obtained from each company's press releases. Appendix 5 provides a full list of M&A transaction observed between 2008

and 2012.

2.7. Statistical procedures utilized in this dissertation

This section describes statistical procedures employed in this dissertation. While Relationships between R&D productivity and industry consolidations and therapeutic categories are examined for both Japanese and global pharmaceutical companies, relationships between the decline of R&D productivity and industry consolidations and therapeutic categories are additionally examined for the Japanese case.

2.7.1. Statistical analysis on Japanese pharmaceutical industry

To verify a relationship between the decline of R&D productivity from 1980 and 1997 based on the Malmquist index and industry consolidations, a Bartlett test of homogeneity of variances was conducted to measure any statistical difference among subgroups. Based on these results, a Tukey-Kramer test was carried out to confirm any statistical significance. In order to verify relationships between R&D productivity and industry consolidations and therapeutic category in 1997 were analyzed with Mann-Whitney U tests.

2.7.2. Statistical analysis on global pharmaceutical industry

In order to verify a relationship between each R&D productivity scores and M&A, the multiple regression analysis is applied. After constructing the

RDP map and calculating the R&D productivity scores, a relationship between R&D productivity and therapeutic category for 2007 and 2012 data were analyzed with Mann-Whitney U tests.

2.8. Summary

Among many approaches to measure R&D productivity, the RDP map approach is selected at least for two reasons. First, values of the RDP map were calculated based on DEA which provides the relative score, or a distance from the industry benchmark. DEA is particularly suitable for measuring the pharmaceutical R&D productivity because the model does not assume a linear relationship between R&D spending and the number of NMEs. DEA also does not involve a data normalization process that does not require an explicit specification of inputs and outputs. Second, the RDP map utilizes the concept of decomposition of R&D productivity based on an idea introduced by Paul et al. [23] They decomposed R&D productivity into two constituent ratios: The R&D efficiency (cost per NME), and R&D effectiveness (product value per NME). Their model is short of explaining impacts from each stage on the overall R&D productivity and it is not on an individual company basis.

3. Analysis on Japanese pharmaceutical companies between 1980 and 2006

This chapter attempts to investigate determinants of the R&D productivity decline observed between 1980 and 1997, and relationships between the R&D productivity and industry consolidations and therapeutic categories in 1997. The RDP map for 2003 and 2006 were also provided to illustrate R&D productivity of individual companies.

3.1. Results on R&D productivity among Japanese pharmaceutical industry

This section provides results of R&D productivity and these relationships. First, results from several R&D productivity measurement models are explained. Based on these outcomes, statistical outcomes from relationships between R&D productivity and industry consolidations and therapeutic categories are provided.

3.1.1. Results on R&D productivity

Table 3.1 compares DEA scores from three approaches for 15 Japanese pharmaceutical companies in 1997. DEA scores based on the conventional calculation show that Sankyo, Takeda and Tokyo Tanabe were efficient. Other two decomposition models illustrate different results. The separate model, which does not utilize the intermediary, shows that only Takeda achieved overall efficiency in both cost efficiency and product value

effectiveness. Five out of 15 companies (Daiichi, Takeda, Sankyo, Tokyo Tanabe, and Yamanouchi) were cost efficient and three (Chugai, Sankyo, Takeda) had optimal in product value effectiveness. R&D productivity model, which utilizes the intermediary, shows that Takeda achieved overall efficiency in both cost efficiency and product value effectiveness again. Five out of 15 companies (Eisai, Fujisawa, Sankyo, Shionogi, and Yamanouchi) were not cost efficient and two (Sankyo and Takeda) had optimal in product value effectiveness.

Table 3.1. Comparison of DEA scores of 15 Japanese companies in 1997

	Conventional DEA	Separate Model		R&D Productivity Model	
	R&D Productivity	Cost Efficiency Index	Product Value Effectiveness Index	Cost Efficiency Index	Product Value Effectiveness Index
Chugai	0.768	0.565	1	1	1.960
Daiichi	0.865	1	1.685	1	1.685
Dainippon	0.991	0.957	1.508	1	1.586
Eisai	0.774	0.620	1.197	0.852	1.591
Fujisawa	0.745	0.699	1.421	0.891	1.754
Kaken	0.971	0.992	1.623	1	1.641
Nippon Shinyaku	0.900	0.888	1.387	1	1.809
Sankyo	1	0.703	1	0.703	1
Shionogi	0.784	0.944	1.769	0.944	1.769
Takeda	1	1	1	1	1
Tanabe	0.842	0.764	1.395	1	1.795
Tokyo Tanabe	1	1.000	1.559	1	1.559
Toyama Chemical	0.923	1.000	1.768	1	1.768
Yamanouchi	0.890	0.952	1.433	0.885	1.412
Yoshitomi	0.938	1	1.706	1	1.706

Table 3.2 compares the actual number of NMEs with the optimized number of NMEs for each company in 1997. Eight out of 15 companies had the same number of actual weighted NMEs with the optimized NMEs which were used to calculate the R&D productivity model. Chugai had the largest difference between the actual and the optimized number of weighted NMEs. Chugai developed the weighted adjusted NMEs of 4.5 while a company with

the same R&D spending developed 17.6 NMEs. Eisai, Fujisawa, and Tanabe also developed a fewer NMEs compared with the optimized NMEs. Only Yamanouchi had the lower number of optimized NMEs than the actual number. Figure 3.1 depicts the accumulated R&D spending, actual, adjusted, and optimized number of NMEs for Japanese pharmaceutical companies in 1997.

Table 3.2. Comparison of the actual, adjusted and optimized number of NMEs for each Japanese company in 1997

Name	# of NMEs			Difference
	Actual	Adjusted	Optimized	
Chugai	6	4.5	17.6	13.1
Nippon Shinyaku	7	4.5	7.7	3.2
Tokyo Tanabe	9	5.2	5.2	0.0
Toyama Chemical	9	7.0	7.0	0.0
Kaken	11	6.9	7.1	0.2
Tanabe	14	10.5	16.3	5.8
Dainippon	15	9.7	10.7	1.0
Eisai	15	11.0	18.2	7.2
Yoshitomi	15	10.4	10.4	0.0
Fujisawa	18	12.5	18.2	5.7
Sankyo	22	14.9	14.9	0.0
Takeda	25	23.0	23.0	0.0
Daiichi	26	18.2	18.2	0.0
Yamanouchi	26	18.7	18.2	-0.5
Shionogi	29	18.2	18.2	0.0

Figure 3.1. Accumulated R&D spending, actual, adjusted, and optimized number of NMEs for Japanese pharmaceutical companies in 1997

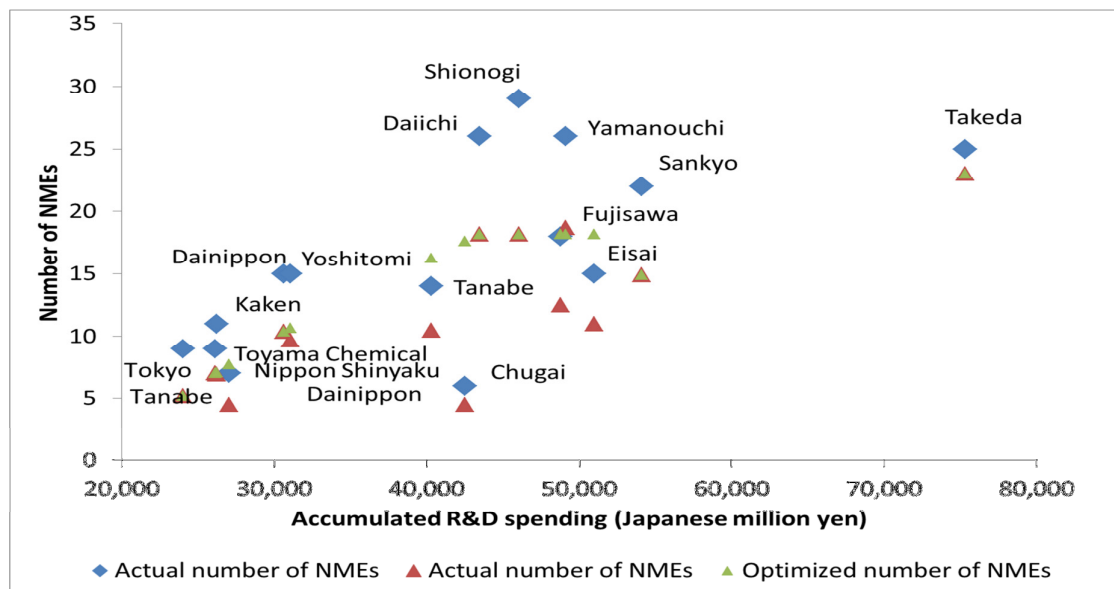


Figure 3.2 and Figure 3.3 depict the accumulated sales and operating profits from 1980 to 1997 compared with actual, adjusted, and optimized number of NMEs, respectively.

Figure 3.2. Accumulated sales, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 1997

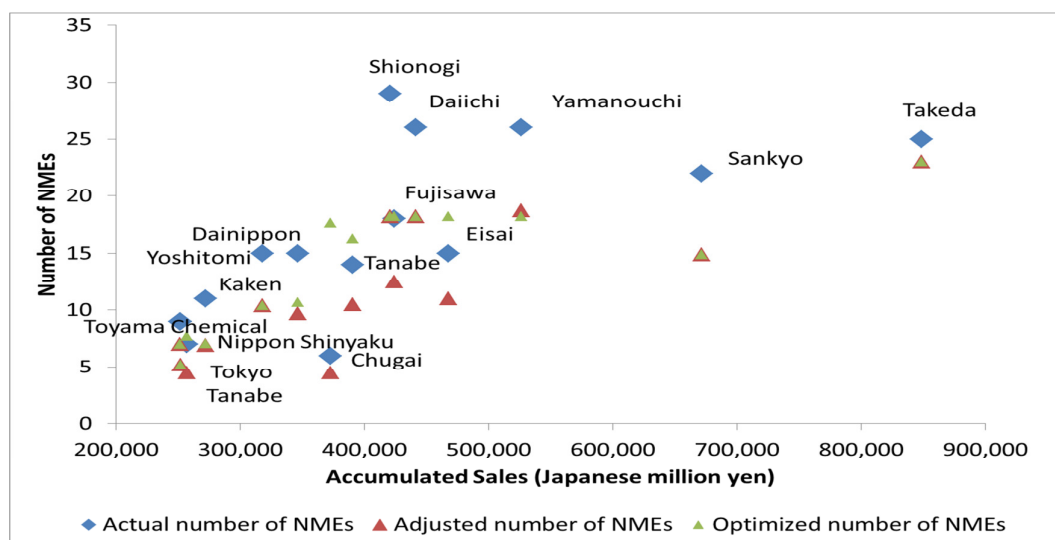


Figure 3.3. Accumulated operating profits, actual, adjusted, and optimized

number of NMEs among Japanese pharmaceutical companies from 1980 to 1997

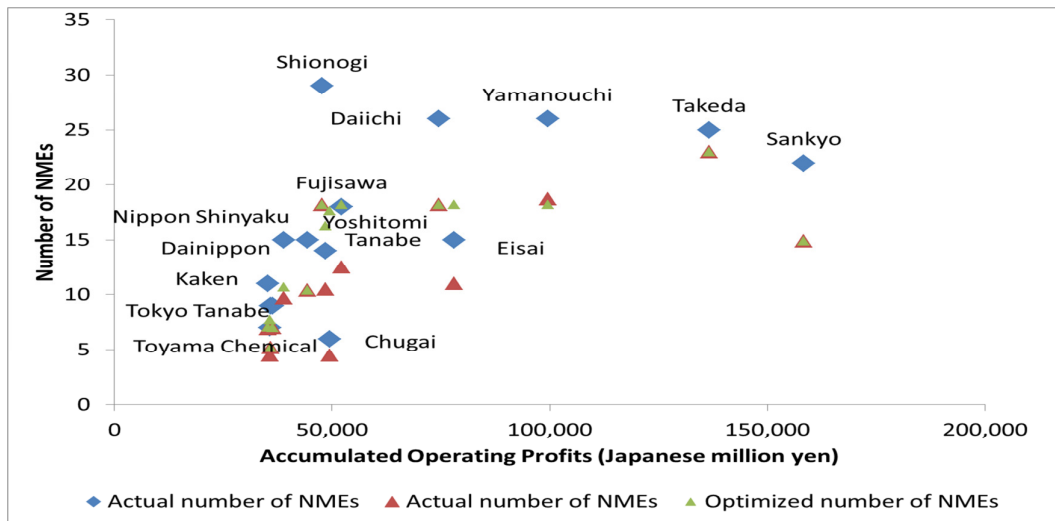


Table 3.3 compares DEA scores from three approaches for 11 Japanese pharmaceutical companies in 2003. DEA scores based on the conventional calculation show that Dainippon, Kaken, Takeda and Yamanouchi were efficient. Models based on decomposition of R&D productivity illustrate different results. The separate model, which does not utilize the intermediary, shows that only Takeda achieved overall efficiency. Four out of 11 companies (Daiichi, Kaken, Takeda, and Yamanouchi) were cost efficient and three (Eisai, Nippon Shinyaku, and Takeda) had optimal in product value effectiveness. R&D productivity model, which utilizes the intermediary, shows that only Takeda achieved overall efficiency. Three out of 11 companies (Eisai, Fujisawa, and Sankyo) were not cost efficient and one (Takeda) had optimal in product value effectiveness.

Table 3.3. Comparison of DEA scores of 15 Japanese companies in 2003

	Conventional DEA	Separate Model		R&D Productivity Model	
	R&D Productivity	Cost Efficiency Index	Product Value Effectiveness Index	Cost Efficiency Index	Product Value Effectiveness Index
Dainippon	1	0.792	2.007	1	2.435
Kaken	1	1	3.506	1	3.506
Takeda	1	1	1	1	1
Yamanouchi	1	1	1.765	1	1.765
Sankyo	0.925	0.560	1.162	0.798	1.513
Eisai	0.894	0.434	1	0.912	1.804
Nippon Shinyaku	0.821	0.821	1	1	5.779
Daiichi	0.811	1	2.438	1	2.438
Fujisawa	0.720	0.533	1.503	0.911	2.282
Tanabe	0.559	0.709	2.980	1	3.973
Shionogi	0.462	0.752	3.498	1	4.337

Figure 3.4 depicts the accumulated R&D spending from 1980 to 2003, actual, adjusted, and optimized number of NMEs for Japanese pharmaceutical companies in 2003.

Table 3.4. Comparison of the actual number of NMEs with the optimized number of NMEs for each company in 2003

Name	# of NMEs			Difference
	Actual	Adjusted	Optimized	
Nippon Shinyaku	8	3.3	8.6	5
Kaken	12	7.7	7.7	0
Dainippon	16	9.6	11.2	2
Eisai	17	13.0	22.4	9
Tanabe	19	13.4	17.4	4
Fujisawa	21	15.2	22.4	7
Sankyo	25	17.5	22.4	5
Daiichi	29	19.7	19.7	0
Shionogi	29	17.7	21.6	4
Takeda	31	26.7	26.7	0
Yamanouchi	31	22.4	22.4	0

Figure 3.4. Accumulated R&D spending, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies in 2003

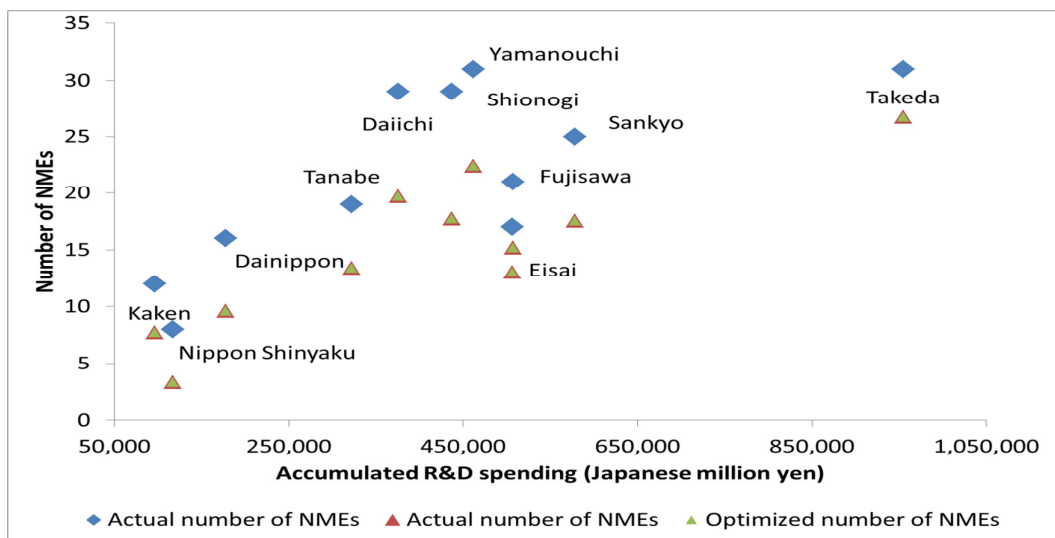


Figure 3.5 and Figure 3.6 depict the accumulated sales and operating profits from 1980 to 2003 compared with actual, adjusted, and optimized number of NMEs, respectively.

Figure 3.5. Accumulated sales, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 2003

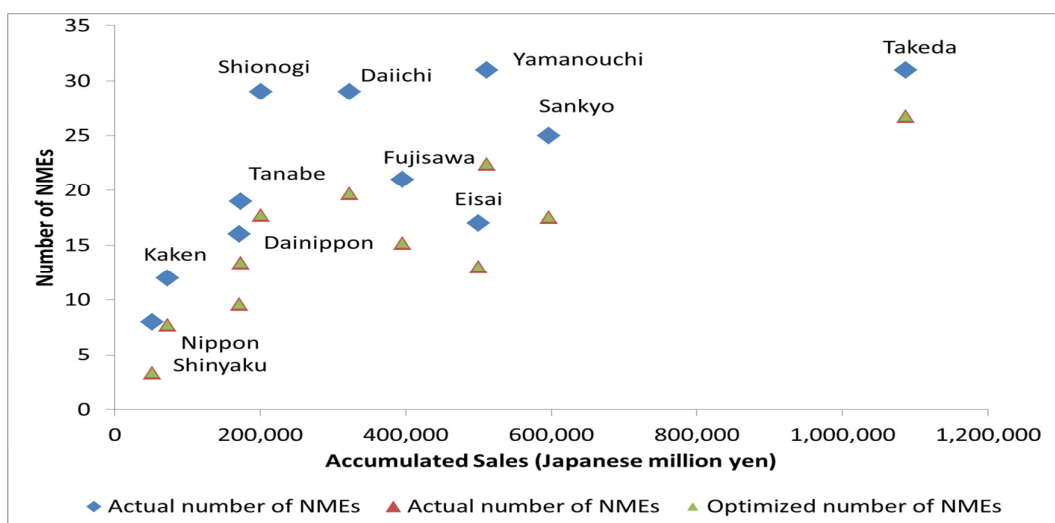


Figure 3.6. Accumulated operating profits, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 2003

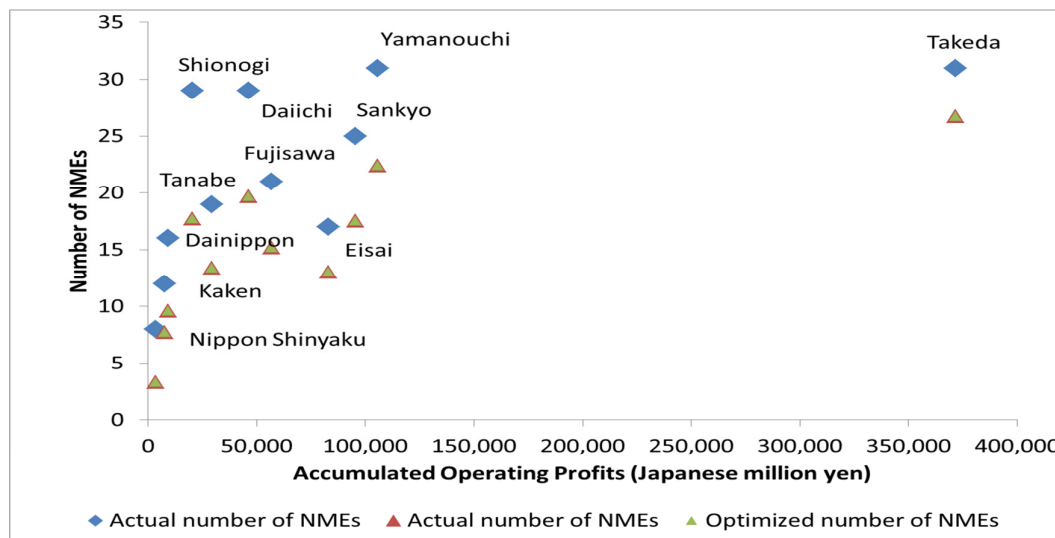


Table 3.5 compares DEA scores from three approaches for 8 Japanese pharmaceutical companies in 2006. DEA scores based on the conventional calculation show that Kaken and Takeda were efficient. Other two models illustrate different results. The separate model, which does not utilize the intermediary, shows that none achieved overall efficiency. Four out of 8 companies (Astellas, Daiichi Sankyo, Kaken and Shionogi) were cost efficient and three (Eisai, Nippon Shinyaku, and Takeda) had optimal in product value effectiveness. R&D productivity model, which utilizes the intermediary, shows that none also achieved overall efficiency in both cost efficiency and product value effectiveness. Three out of 8 companies (Astellas, Daiichi Sankyo, and Takeda) were not cost efficient and only Takeda had optimal in product value effectiveness.

Table 3.5. Comparison of DEA scores of 15 Japanese companies in 2007

	Conventional DEA	Separate Model		R&D Productivity Model	
	R&D Productivity	Cost Efficiency Index	Product Value Effectiveness Index	Cost Efficiency Index	Product Value Effectiveness Index
Astellas	0.730	1	1.342	0.645	1.342
Daiichi Sankyo	0.658	1	1.483	0.639	1.483
Eisai	0.999	0.464	1	1	1.644
Kaken	1	1	4.404	1	4.404
Nippon Shinyaku	0.771	0.771	1	1	7.023
Shionogi	0.434	1	4.716	1	4.716
Takeda	1	0.666	1	0.666	1
Tanabe	0.533	0.907	4.104	1	4.357

Table 3.6 compares the actual number of NMEs with the optimized number of NMEs for each company in 2006. Three out of 8 companies had the same number of actual and the optimized number of weighted NMEs. Eisai had the largest difference between actual number and the optimized number of weighted NMEs followed by Nippon Shinyaku. Eisai developed the actual number of weighted NMEs of 13 while a company with the same R&D spending developed 22.6 NMEs. Tanabe also developed a fewer NMEs. Both Astellas and Daiichi Sankyo had the lower number of optimized NMEs than the actual number. Figure 3.7 depicts the accumulated R&D spending, actual, adjusted, and optimized number of NMEs for Japanese pharmaceutical companies in 2003.

Table 3.6. Comparison of the actual number of NMEs with the optimized number of NMEs for each company in 2006

Name	# of NMEs			Difference
	Actual	Adjusted	Optimized	
Nippon Shinyaku	8	3.3	8.6	5
Kaken	13	7.7	7.7	0
Eisai	17	13.0	22.6	10
Tanabe	20	14.2	15.2	1
Shionogi	32	18.9	18.9	0
Takeda	33	26.9	26.9	0
Astellas	53	38.9	26.9	-12
DaiichiSankyo	57	39.2	26.9	-12

Figure 3.7. Accumulated R&D spending, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies in 2006

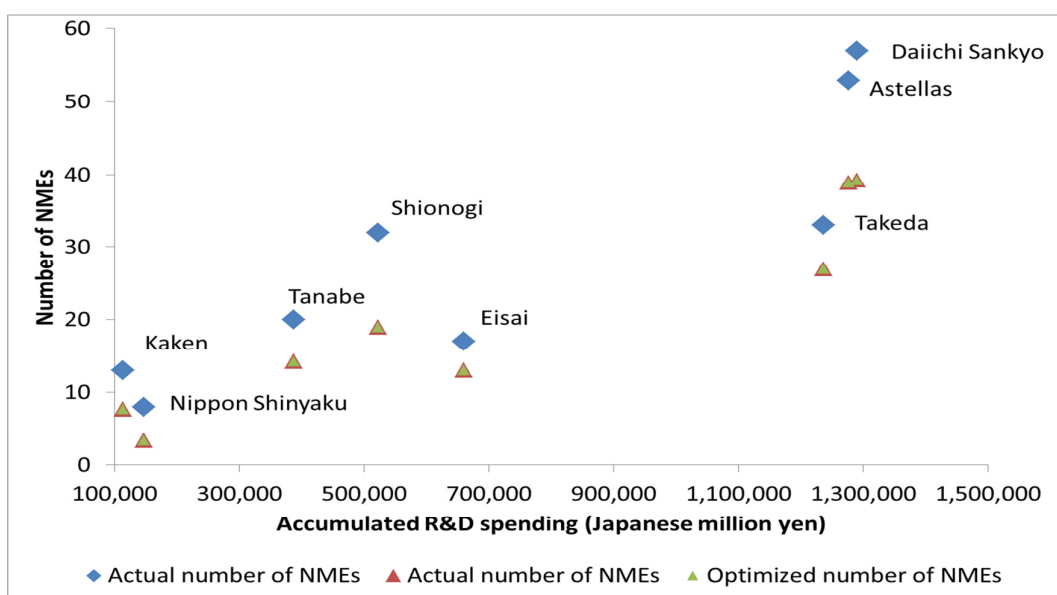


Figure 3.8 and Figure 3.9 depict the accumulated sales and operating profits from 1980 to 2006 compared with actual, adjusted, and optimized number of NMEs, respectively.

Figure 3.8. Accumulated sales, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 2006

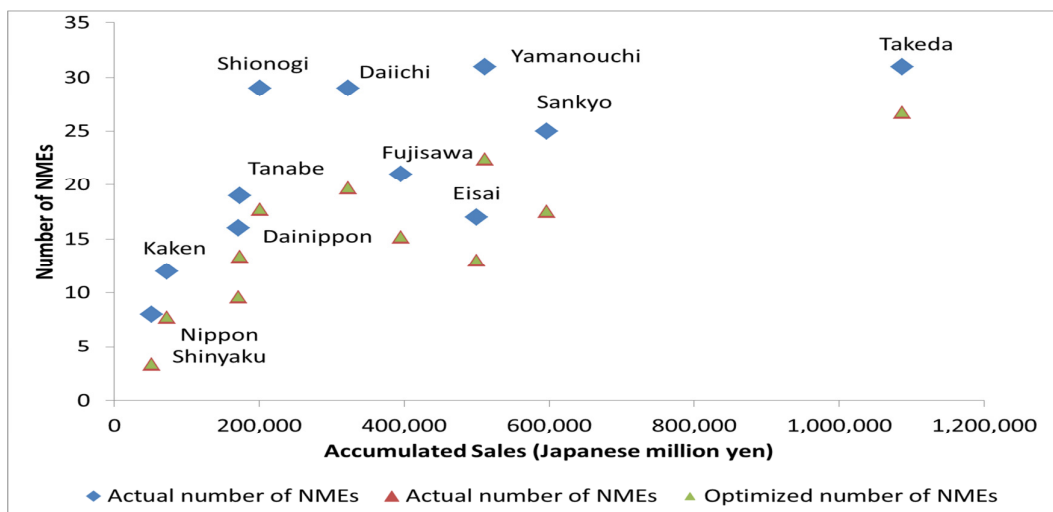


Figure 3.9. Accumulated operating profits, actual, adjusted, and optimized number of NMEs among Japanese pharmaceutical companies from 1980 to 2006

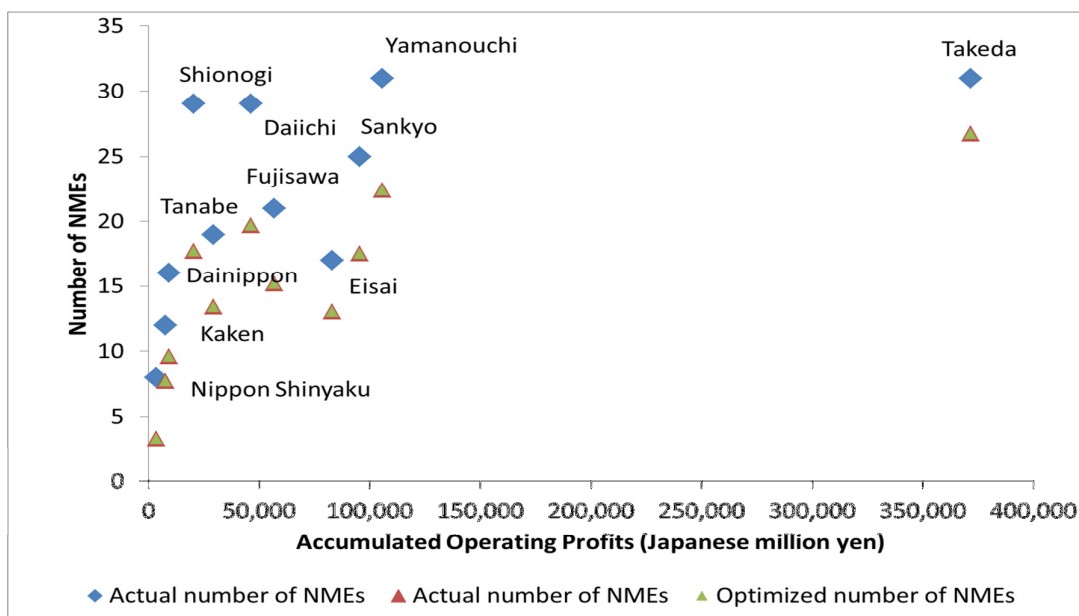


Table 3.7 shows that the R&D productivity of the 15 Japanese companies declined from 1980 to 1997 and R&D productivity for all companies were

deteriorated. The industry required 2.102 times higher R&D spending in 1997 to generate the same level of output in 1980 in average (MI score = 2.102). Among 15 companies, Chugai with the MI score of 3.187 had the worst decline, or R&D productivity of Chugai in 1997 was deteriorated 3.187 times compared with the 1980 level. Shionogi with the MI score of 1.399 had the least decline of R&D productivity, or Shionogi required 39.9% more R&D spending to sustain the output level in 1980.

Table 3.7. MI score of the R&D productivity for 15 Japanese companies from 1980 to 1997 by company

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Yoshitomi	0.776	0.896	0.917	1.165	1.308	1.304	1.391	1.256	1.229	1.203	1.224	1.305	1.337	1.420	1.449	1.499	1.569
Daiichi	0.880	0.872	0.934	1.023	1.085	1.052	1.096	1.172	1.250	1.401	1.413	1.377	1.328	1.417	1.482	1.538	1.614
Toyama Chemical	0.960	1.053	1.245	1.555	1.600	1.609	1.500	1.601	1.563	1.705	1.750	1.819	1.793	1.965	2.090	2.192	2.290
Yamanouchi	0.984	1.069	0.993	1.107	1.094	1.059	0.968	1.008	1.046	1.137	1.178	1.164	1.225	1.312	1.422	1.433	1.512
Sankyo	1.003	1.070	1.218	1.410	1.350	1.348	1.450	1.476	1.532	1.662	1.754	1.799	1.843	1.958	2.052	2.005	2.053
Dainippon	1.016	1.067	1.129	1.360	1.335	1.313	1.117	1.114	1.142	1.221	1.235	1.297	1.328	1.430	1.547	1.571	1.677
Shionogi	1.020	0.976	1.131	1.368	1.260	1.239	1.152	1.151	1.165	1.273	1.231	1.225	1.248	1.302	1.347	1.395	1.399
Takeda	1.041	1.118	1.216	1.392	1.565	1.609	1.480	1.491	1.563	1.689	1.744	1.729	1.915	1.934	1.946	2.027	2.146
Kaken	1.092	1.050	1.115	1.383	1.430	1.227	1.306	1.297	1.418	1.519	1.263	1.315	1.443	1.539	1.663	1.753	1.860
Tokyo Tanabe	1.095	1.052	1.286	1.596	1.671	1.384	1.262	1.372	1.533	1.587	1.702	1.821	2.033	2.184	2.316	2.415	2.568
Nippon Shinyaku	1.103	1.200	1.389	1.700	1.918	1.833	1.873	1.826	1.927	2.121	2.223	2.253	2.344	2.279	2.414	2.438	2.693
Eisai	1.114	1.163	1.392	1.720	1.830	1.581	1.582	1.619	1.758	1.867	1.994	2.042	2.228	2.282	2.277	2.403	2.416
Tanabe	1.120	1.160	1.318	1.570	1.738	1.535	1.363	1.409	1.514	1.619	1.716	1.788	1.767	1.787	1.869	1.938	2.044
Chugai	1.131	1.230	1.396	1.697	1.825	1.789	1.735	1.903	2.038	2.344	2.398	2.464	2.628	2.703	2.567	2.917	3.187
Fujisawa	1.229	1.279	1.582	2.004	2.477	2.244	2.043	1.961	1.914	1.975	1.989	1.984	2.056	2.073	2.255	2.352	2.499
Average	1.038	1.084	1.217	1.470	1.566	1.475	1.421	1.444	1.506	1.622	1.654	1.692	1.768	1.839	1.913	1.992	2.102

Table 3.8 and 3.9 show breakdown of MI score of the R&D productivity of the 15 Japanese companies. Table 3.8 shows that there was wider dispersion of EC scores among companies. Since the average EC score in 1997 was 1.002, the industry in general managed to catch up the

deterioration of the industry productivity. Shionogi had the lowest EC score of 0.750 and Fujisawa had the highest score of 1.322. Since the EC score measures changes in how companies catch up to the industry benchmark from one period to another, Shionogi made much efforts and ability to catch up the benchmark was 25% better than the level in 1980. Fujisawa, on the other hand, made little efforts to catch up to the benchmark or their R&D productivity to meet the industry benchmark was declined by 32.2%.

Table 3.8. EC score of the R&D productivity for 15 Japanese companies from 1980 to 1997 by company

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Yoshitomi	0.802	0.819	0.808	0.881	0.975	1.001	0.998	0.941	0.918	0.837	0.827	0.864	0.852	0.838	0.809	0.800	0.790
Toyama Chemical	0.927	0.927	0.927	0.969	1.038	1.128	1.122	1.124	1.161	1.105	1.134	1.142	1.077	1.129	1.129	1.139	1.120
Yamanouchi	0.955	0.941	0.829	0.830	0.850	0.877	0.819	0.819	0.819	0.819	0.819	0.819	0.819	0.819	0.825	0.819	0.820
Daiichi	1.000	1.000	1.000	1.000	1.000	1.000	1.013	1.016	1.067	1.069	1.062	1.037	1.000	1.000	1.000	1.000	1.000
Sankyo	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.036	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Eisai	1.007	0.967	0.988	1.092	1.117	1.137	1.121	1.113	1.185	1.166	1.205	1.255	1.250	1.200	1.159	1.181	1.167
Kaken	1.011	0.946	0.914	0.952	0.977	0.949	0.933	0.903	0.937	0.891	0.805	0.801	0.813	0.803	0.823	0.837	0.841
Shionogi	1.012	0.852	0.858	0.881	0.865	0.875	0.864	0.851	0.863	0.854	0.816	0.801	0.802	0.783	0.785	0.781	0.753
Nippon Shinyaku	1.018	0.974	1.018	1.036	1.053	1.046	1.025	1.030	1.042	1.037	1.053	1.088	1.055	1.039	1.020	1.032	1.058
Tanabe	1.021	0.958	0.974	0.965	0.991	0.961	0.906	0.876	0.911	0.892	0.904	0.966	1.009	0.990	0.997	0.985	0.984
Tokyo Tanabe	1.028	0.971	1.042	1.082	1.066	1.042	0.965	0.992	1.072	1.024	1.045	1.082	1.118	1.106	1.083	1.078	1.087
Chugai	1.032	0.981	0.961	0.948	0.977	1.080	1.066	1.117	1.172	1.205	1.231	1.276	1.237	1.196	1.062	1.204	1.244
Dainippon	1.040	0.997	0.991	1.005	1.002	0.919	0.882	0.883	0.865	0.830	0.805	0.815	0.805	0.804	0.817	0.807	0.813
Takeda	1.078	1.085	1.077	1.090	1.103	1.115	1.013	1.000	1.027	1.072	1.076	1.084	1.119	1.090	1.053	1.044	1.041
Fujisawa	1.170	1.076	1.214	1.286	1.458	1.521	1.457	1.393	1.406	1.314	1.282	1.301	1.296	1.250	1.302	1.302	1.316
Average	1.007	0.966	0.973	1.001	1.032	1.043	1.012	1.004	1.032	1.008	1.004	1.022	1.017	1.003	0.991	1.001	1.002

Table 3.9 shows that there was dispersion of FS scores among companies. Since the average FS score in 1997 was 2.083, the industry benchmark was deteriorated from 1980 to 1997. Since the FS score measures changes in the efficient frontier, an industry-based R&D productivity benchmark was down

by 2.083 times or the industry needed to almost twice more R&D spending to achieve the level found in 1980. Daiichi had the lowest EC score of 0.750 and Chugai had the highest score of 1.32.

Table 3.9. FS score of the R&D productivity for 15 Japanese companies in 1997

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Daiichi	0.880	0.872	0.934	1.023	1.085	1.052	1.082	1.153	1.172	1.310	1.331	1.328	1.328	1.417	1.482	1.538	1.614
Takeda	0.965	1.030	1.130	1.277	1.420	1.443	1.461	1.491	1.522	1.575	1.621	1.595	1.712	1.775	1.848	1.943	2.061
Yoshitomi	0.967	1.094	1.135	1.322	1.341	1.302	1.394	1.334	1.340	1.438	1.480	1.511	1.569	1.695	1.791	1.873	1.985
Dainippon	0.977	1.070	1.139	1.353	1.332	1.429	1.267	1.262	1.321	1.471	1.534	1.592	1.650	1.778	1.893	1.948	2.063
Sankyo	1.003	1.070	1.218	1.410	1.350	1.348	1.450	1.476	1.479	1.662	1.754	1.799	1.843	1.958	2.052	2.005	2.053
Shionogi	1.007	1.146	1.319	1.553	1.456	1.416	1.333	1.352	1.349	1.492	1.509	1.529	1.555	1.662	1.716	1.786	1.858
Yamanouchi	1.030	1.136	1.198	1.334	1.287	1.208	1.183	1.231	1.277	1.388	1.438	1.421	1.495	1.602	1.724	1.750	1.842
Toyama Chemical	1.036	1.136	1.342	1.605	1.542	1.426	1.337	1.424	1.346	1.543	1.544	1.593	1.664	1.741	1.852	1.924	2.044
Fujisawa	1.051	1.189	1.303	1.558	1.698	1.475	1.402	1.407	1.361	1.503	1.551	1.524	1.587	1.659	1.732	1.806	1.899
Tokyo Tanabe	1.066	1.084	1.234	1.476	1.567	1.328	1.308	1.383	1.430	1.550	1.628	1.683	1.819	1.975	2.139	2.241	2.362
Kaken	1.080	1.110	1.220	1.453	1.464	1.293	1.400	1.437	1.514	1.705	1.570	1.642	1.776	1.917	2.022	2.095	2.213
Nippon Shinyaku	1.083	1.231	1.364	1.641	1.821	1.753	1.828	1.772	1.849	2.045	2.111	2.072	2.223	2.194	2.366	2.361	2.546
Chugai	1.096	1.254	1.453	1.790	1.867	1.657	1.627	1.704	1.738	1.946	1.948	1.932	2.125	2.261	2.416	2.423	2.561
Tanabe	1.097	1.210	1.353	1.626	1.754	1.597	1.504	1.608	1.662	1.814	1.897	1.852	1.751	1.805	1.875	1.967	2.077
Eisai	1.106	1.203	1.409	1.575	1.639	1.390	1.411	1.455	1.484	1.602	1.655	1.627	1.782	1.902	1.966	2.036	2.070
Average	1.030	1.122	1.250	1.466	1.508	1.408	1.399	1.433	1.456	1.603	1.638	1.647	1.725	1.823	1.925	1.980	2.083

3.1.2. Results on relationships between R&D productivity and industry consolidation

Table 3.10 illustrates that the results of the Mann Whitney U test applied to the relationships between cost efficiency and industry consolidation revealed a statistically significant difference ($P=0.016$) and the relationships between product value effectiveness and industry consolidation revealed a statistically significant difference ($P<0.001$). An examination of the averages of each components of R&D productivity and

industry consolidation demonstrates that the companies which involved in the industry consolidation were relatively optimal in cost efficiency and relatively less optimal in product value effectiveness since the company's DEA scores becomes 1 when they achieves the efficiency level.

Table 3.10. Statistical results on relationships between R&D productivity and industry consolidation

		Cost Efficiency Index				Product Effectiveness Index		
		n	Average	z-score	p-value	Average	z-score	p-value
Industry Consolidation	Yes	4	0.920	1.787	0.016**	1.082	4.208	<0.001***
	No	11	0.914			1.024		

Source: Shimura H., Masuda S., Kimura H. [53]

3.1.3. Results on relationships between R&D productivity and therapeutic categories

In this subsection, the results from relationships between the deterioration of R&D productivity by the Malmquist Index and therapeutic categories were provided followed by the results from relationships between R&D productivity and therapeutic categories. The results of the ANOVA tests using the MI scores (Table 3.11) show that the changes in R&D productivity differed among companies that developed antibiotics in the 1980s (p-value =0.010) and among companies that developed different antibiotics subclasses, that is, '613 and '624 (p-value = 0.011). Table 3.12 shows that antibiotics approvals in the 1980s explained the dispersion of R&D

productivity deterioration, but companies' approaches toward antibiotics (i.e., internally or using licensing activities) did not explain the dispersion. Furthermore, Table 3.13 shows that the similar result but a shift from one subclass to another was not a factor.

Table 3.11. Statistical results on the R&D productivity using the MI scores

	Barlett Testing	ANOVA
Size Effect	0.376	0.768
Antibiotics Approval in 1980s	0.811	0.010***
Lifestyle diseases drug approval in 1980s	0.818	0.579
Digestive drug approval in 1980s	0.407	0.823
Antibiotics approval in 1980s and 1990s	0.696	0.914
Antibiotics Subclasses	0.347	0.011**

Source: Shimura H., Masuda S., Kimura H. [53]

Table 3.12. Statistical results on antibiotics development strategy by style

		Tukey-Kramer		
		Subgroup 1	Subgroup 2	Subgroup 3
Subgroup 1	No antibiotics approval in 1980s	-	-	-
Subgroup 2	Approved licenced-in antitobioics in 1980s	0.017**	-	-
Subgroup 3	Approved internally developed antibiotics in 1980s	0.007***	0.758	-

Source: Shimura H., Masuda S., Kimura H. [53]

Table 3.13. Statistical results on antibiotics development strategy by subclass

		Tukey-Kramer			
		Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
Subgroup 1	No antibiotics approval in 1980s	-	-	-	-
Subgroup 2	Approved antibiotics subclass of '613 only	0.025**	-	-	-
Subgroup 3	Approved antibiotics subclass of '624 only	0.028**	0.716	-	-
Subgroup 4	Approved antibiotics subclass of '613and '624	0.073*	0.944	0.981	-

Source: Shimura H., Masuda S., Kimura H. [53]

Table 3.14 illustrates that the results of the Mann Whitney U test applied to the relationships between cost efficiency and four therapeutic categories

revealed a statistically significant difference with antibiotics (P=0.076) and lifestyle disease developers (P<0.001) and the relationships between product value effectiveness and four categories revealed a statistically significant difference (P<0.001 except CNS (P=0.002)). An examination of the averages of each components of R&D productivity and therapeutic categories demonstrates that the companies which involved in four therapeutic categories were relatively optimal in product value effectiveness and companies which involved in lifestyle diseases were relatively less optimal in product effectiveness since the company's DEA scores becomes 1 when they achieves the efficiency level.

Table 3.14. Statistical results on relationships between R&D productivity and therapeutic categories in 1997

Therapeutic Franchise		Cost Efficiency Index				Product Effectiveness Index		
		n	Average	z-score	p-value	Average	z-score	p-value
Antibiotics	Developer	11	0.917	1.776	0.076*	1.030	3.627	<0.001***
	Non-Developer	4	0.913			1.065		
Digestive system	Developer	9	0.912	0.555	0.579	1.022	3.785	<0.001***
	Non-Developer	6	0.922			1.065		
Central nervous system	Developer	9	0.920	0.000	1.000	1.021	3.877	0.002**
	Non-Developer	7	0.911			1.060		
Lifestyle Disease	Developer	12	0.905	4.572	<0.001***	1.020	3.561	<0.001***
	Non-Developer	3	0.958			1.115		

3.1.4. Results on RDP maps

Figure 3.10 and Figure 3.11 illustrate the separate R&D productivity and RDP maps in 1997, respectively. Based on efficiency/inefficiency in cost efficiency and product value effectiveness, each company was classified into

four groups. Takeda on the upper right corner of the RDP map was efficient in both the cost efficiency and the product value effectiveness, or was a benchmark of the Japanese pharmaceutical industry in 1997. Fujisawa, Shionogi, Tanabe, Sankyo, and Eisai were on the left upper side of the map and they were inefficient in the cost efficiency process but efficient in the product value effectiveness. Tokyo Tanabe on the lower right axis was efficient in the cost efficiency but inefficient in the product value effectiveness. Finally, Chugai, Kaken, Toyama Chemical, Dainippon, Daiichi, Yoshitomi, and Nippon Shinyaku were both inefficient in the cost efficiency and product value effectiveness. Three companies (Chugai, Toyama Chemical, and Yoshitomi) out of this group were later acquired by Roche, Taisho, and Mitsubishi Chemical, respectively after 1998.

Figure 3.10. Separate R&D productivity map in 1997

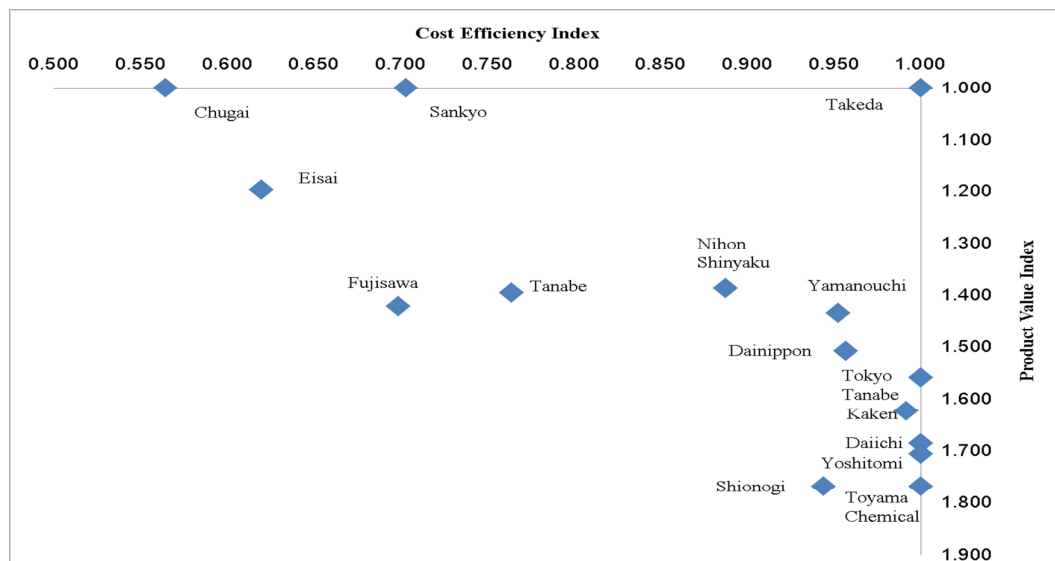


Figure 3.11. RDP map in 1997

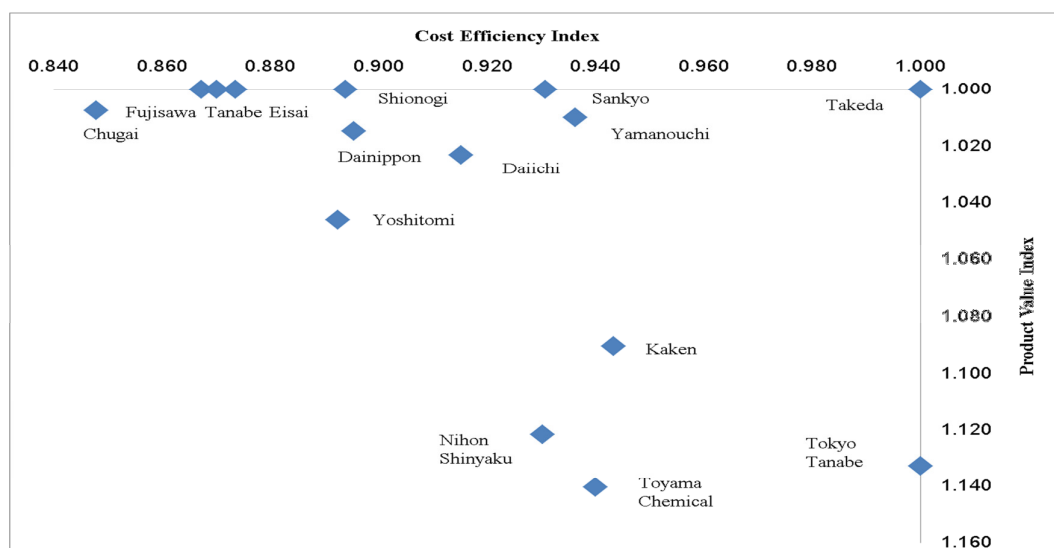


Figure 3.12 and Figure 3.13 illustrate the separate R&D productivity and RDP maps in 2003, respectively. Based on efficiency/inefficiency in cost efficiency and product value effectiveness, each company was classified into three groups, instead of four. Takeda on the upper right corner of the RDP map was efficient in both the cost efficiency and the product value effectiveness, or was a benchmark of the Japanese pharmaceutical industry in 2003. Daiichi, Dainippon, Kaken, Nippon Shinyaku, Shionogi, Tanabe, and Yamanouchi, which were scatter on the right axis, were efficient in the cost efficiency but inefficient in the product value effectiveness. Finally, Eisai, Fujisawa, and Sankyo were both inefficient in the cost efficiency and product value effectiveness. Daiichi, Dainippon, and Yamanouchi which were efficient in the cost efficiency but inefficient in the product value effectiveness were later merged with Sankyo, Sumitomo Chemical, and

Yamanouchi after 2003.

Figure 3.12. Separate R&D productivity map in 2003

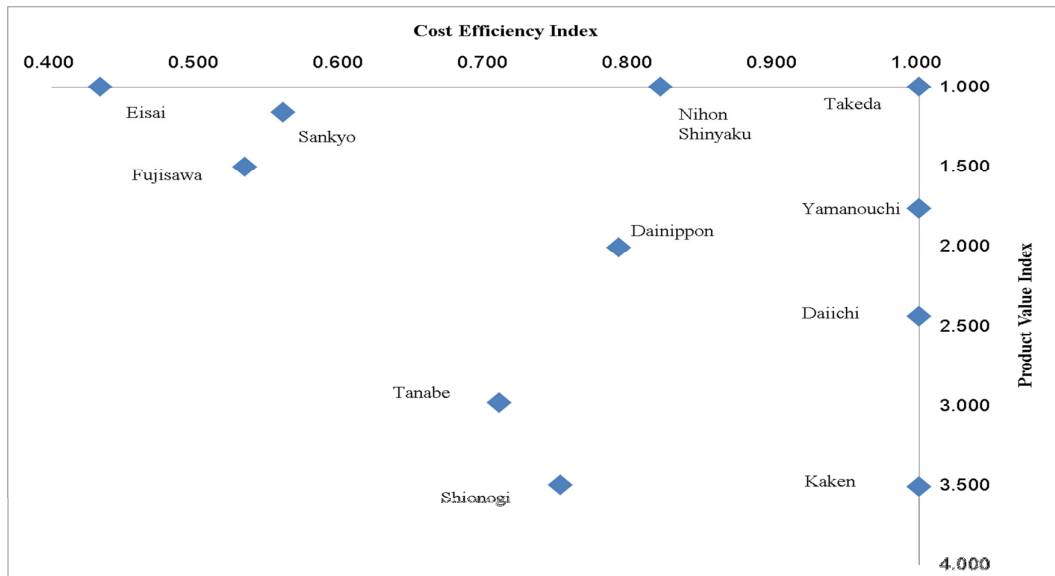


Figure 3.13. RDP map in 2003

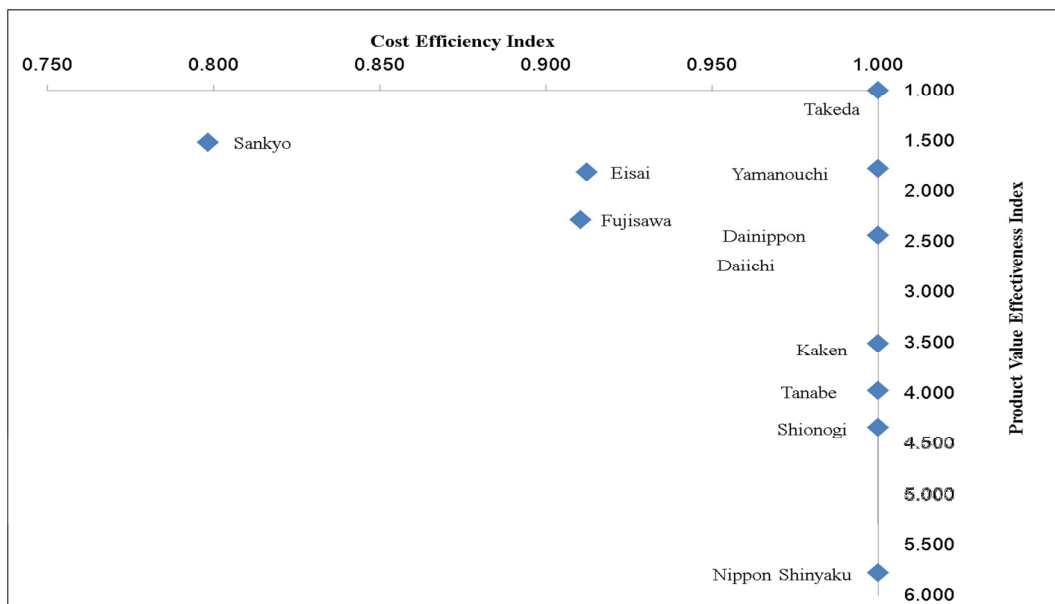


Figure 3.14 and Figure 3.15 illustrate the separate R&D productivity and RDP maps in 2006, respectively. Based on efficiency/inefficiency in cost efficiency and product value effectiveness, each company was classified into

three groups, instead of four. There was no benchmark Japanese pharmaceutical company in 2006. Eisai, Kaken, Nippon Shinyaku, Shionogi, and Tanabe scattered on the right axis, were efficient in the cost efficiency but inefficient in the product value effectiveness. Takeda was inefficient in the cost efficiency process but efficient in the product value effectiveness. Finally, Astellas and Daiichi Sankyo were both inefficient in the cost efficiency and product value effectiveness. Tanabe was later merged with Mitsubishi Chemical.

Figure 3.14. Separate R&D productivity map in 2006

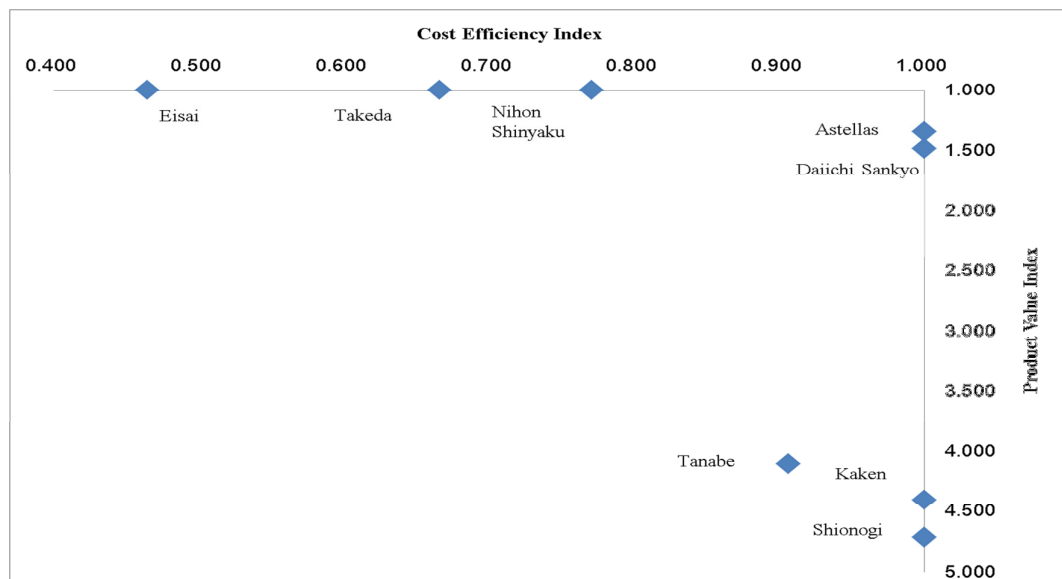


Figure 3.15. RDP map in 2006



3.2. Discussions on analysis on Japanese pharmaceutical analysis

Based on above results, discussions on the R&D productivity of Japanese pharmaceutical companies are made. The R&D productivity model illustrates the R&D productivity issues which a company faces in that time period. Even though there may not be casual relationships, the RDP map enables to visualize the current status among peers and to foresee the corporate behaviors in order to either sustain or improve the R&D productivity.

3.2.1. Discussions on R&D productivity

R&D deterioration among Japanese pharmaceutical company using the Malmquist index reveals that findings are similar to those of Hashimoto and Haneda [20] while they employed the number of patents as an input

variable. The deterioration was mainly due to the decline of the industry benchmark (FS score = 2.08) and the efforts of companies to catch up (EC score = 1.01) were also observed.

R&D productivity model selects companies with a possible inherent risk of relying on small number of NMEs. Decomposition of R&D productivity, indeed, enables to measure R&D productivity with consideration of inherent risks but an interpretation of intermediary is needed to be explained. For example, in 1997, Dainippon had 0.792 and 2.007 under the separate model but 1 and 2.435 under the R&D productivity model. The intermediary for the separate model was 9.6, the actual number of NMEs Dainippon produced. Results from the separate model imply that Dainippon was both inefficient in cost efficiency and product value effectiveness. Thus, Dainippon needed to improve the cost efficiency by either reducing the R&D spending or producing more NMEs or both since comparators produced more NMEs given the same level of R&D spending. At the same time, Dainippon needed to improve the product value effectiveness by reducing the number of NMEs or improving the product value effectiveness (i.e., licensing or additional indication) since comparators had more profitable NMEs. The separate model, however, does not suggest the priority of improvement. For example, if Dainippon decided to produce NMEs with little product values, the cost efficiency should be improved but the product

value effectiveness will be deteriorated further. Thus the overall R&D productivity may not be improved.

The R&D productivity model overcomes this issue using the intermediary. Thus, Dainippon is able to achieve the most efficient R&D productivity with 10.7 NMEs, instead of the actual number of 9.7 NMEs. Since the optimized number of NMEs was higher than the actual number, this results that cost efficiency was inflated and the product value effectiveness was less evaluated. Consequently, the model provides cost efficiency index of 1 and product value effectiveness index of 1.586. Given the current R&D spending, Dainippon needed to produce 10.7 NMEs to reach the benchmark. The R&D productivity model suggests that Dainippon needed to focus on more on product value to balance cost efficiency and product value effectiveness.

3.3. Discussions on relationships between R&D productivity and industry consolidation

Based on R&D deterioration measure using the Malmquist index shows that companies with high MI scores (i.e., their R&D productivity declined relatively significant) were likely merged in a few years though no statistical testing was conducted. For example, Chugai, which had the worst MI score, merged with Roche in 2000. Similarly, Tokyo Tanabe, which had the third-worst MI score, merged with Mitsubishi Chemical in 1999. This finding is consistent with those of LaMattina [17], which suggest that

without an appropriate R&D strategy or improvement of R&D productivity, the industry continues to pursue industry consolidation. Thus, the deterioration of R&D productivity was a possible cause of industry consolidation in the 1990s in Japan, albeit further study may be required to verify the causal relationship between these two phenomena.

The R&D productivity model suggests that companies with less optimal in product value effectiveness or companies with optimal in cost efficiency tended to involve in industry consolidation. In 2001, Chugai which was least optimal in cost efficiency was acquired by Roche. Toyama Chemical with the second lowest product value effectiveness score and Yoshitomi with the third lowest product value effectiveness score were also merged. However, an M&A is not always an appropriate solution since the best fit may not be available at the time of decision making. A company may be able to sustain its R&D productivity by either implementing licensing activities or by eliminating non-core business. For example, Shionogi which was last optimal in product value effectiveness employed licensing activities including licensing-in several antibiotics in 1990s and licensing out rosuvastatin, cholesterol lowering drugs to AstraZeneca. Eisai with the second lowest cost efficiency scores made a strategic alliance for the Alzheimer's drug, Donepezil, with Pfizer in 1994. These events were also supported by a study conducted by Danzon et al [28] who found that the

licensing products tended to increase a higher probability of success, particularly if the licensee was a large firm. Shionogi also spun off its wholesale business unit in 1998. Fujisawa with the fourth-worst MI score withdrew its generic drug business in the United States in 1998.

3.3.1. Discussions on relationships between R&D productivity and therapeutic categories

Deterioration of the R&D productivity was the industry issue and the involvement in the antibiotics R&D was a factor to sustain the R&D productivity for Japanese pharmaceutical companies in 1980s. Among Japanese companies from 1980 to 1997, R&D productivity of companies that developed antibiotics (a dominant category) deteriorated less. Table 3.15 illustrates that while the R&D productivity of companies with no approved antibiotics deteriorated significantly, through licensing activities, they were able to catch up with the industry benchmark with an 18% improvement (EC score = 0.82), and internal efforts to develop antibiotics were slightly helped (EC score = 0.98).

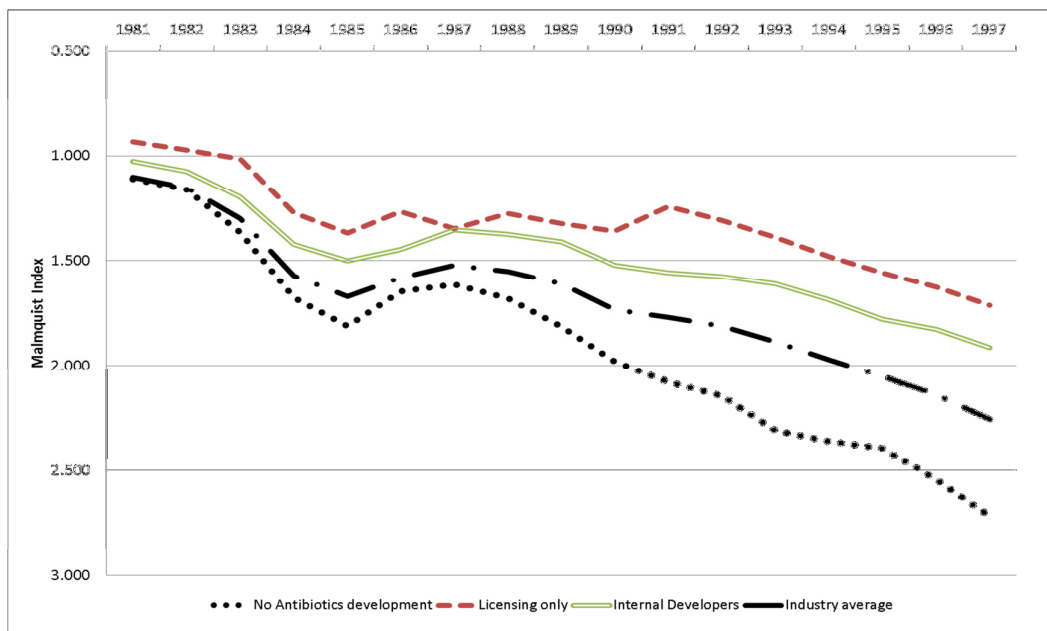
Table 3.15. Average score of MI Index and its components, with subgroups defined by the company's antibiotics development strategy

	Average MI score	Average EC score	Average FS score
Companies with only subclass '624 development	1.65	0.91	1.84
Companies licensed in antibiotics	1.71	0.82	2.10
Companies with both subclass '613 and '624 development	1.84	0.94	1.95
Companies with internally developed antibiotics	1.91	0.98	1.95
Average of companies with only subclass '613 development	1.95	0.97	2.02
Companies with no antibiotics approval product	2.72	1.14	2.38

Source: Shimura H., Masuda S., Kimura H. [53]

The deterioration of R&D productivity has been a major issue in the Japanese pharmaceutical industry and involvement in antibiotics R&D helped sustain R&D productivity of Japanese pharmaceutical companies during the 1980s. Results from the Malmquist index also support argument of licensing activities. Figure 3.16 shows that the R&D productivity of companies utilizing licensing activities deteriorated, although the deterioration from 1980 to 1997 was not statistically significant. These results suggest that licensing activities were more useful than internal development for Japanese companies in sustaining R&D productivity in the 1980s.

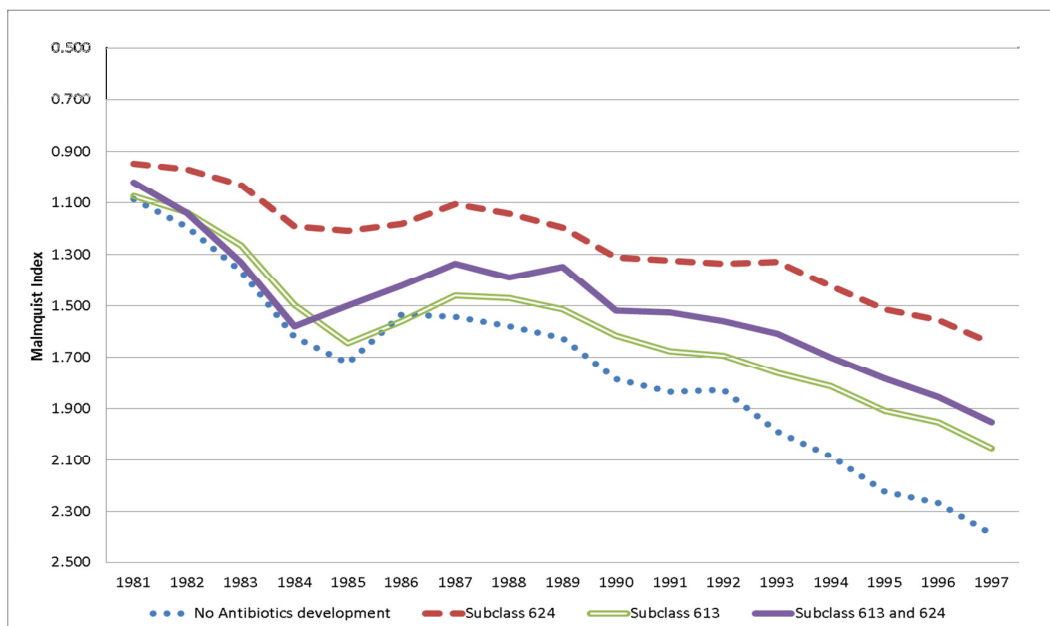
Figure 3.16. Trends of MI indices of the R&D productivity grouped by antibiotics development strategy



Source: Shimura H., Masuda S., Kimura H. [53]

Furthermore, Figure 3.17 shows that the development of a new subclass of antibiotics also helped sustain R&D productivity (EC score = 0.91) even though the Tukey-Kramer test did not show this factor was statistically significant. The development of subclass '613, the dominant subclass in the 1980s, had a marginal impact on the ability to sustain R&D productivity (EC score = 0.97).

Figure 3.17. Trends of MI indices of the R&D productivity grouped by subclass



Source: Shimura H., Masuda S., Kimura H. [53]

Further, based on the RDP map, companies involved in lifestyle disease drug development had less optimal cost efficiency and no other therapeutic categories show a similar result. However, companies with lifestyle disease drugs in their product portfolio were more optimal regarding product value effectiveness versus companies without the drugs. The difference is clearly bigger than in the other three categories. Thus, a company must seek an appropriate balance between cost efficiency and product value effectiveness to maximize its R&D productivity while selecting the appropriate therapeutic categories.

Two lessons can be learned from Japan's case. First, to sustain R&D

productivity over the long term, companies utilized licensing activities and focused on the dominant therapeutic franchises, even on only the most advanced subclass. As antibiotics development case in 1980s and life style diseases in 1990s are observed, therapeutic category selection plays an important role in the company's R&D strategy and impacts on R&D productivity. Second, if a company fails significantly to catch up with the benchmark, it is likely to pursue an M&A or seek an alternative way to improve R&D productivity. Companies with least product effective companies were either acquired or merged. In 1999, Tokyo Tanabe, the least product effective company, was acquired by the Mitsubishi Chemical. Later, companies in the same category, (i.e., Yamanouchi, Daiichi, Dainippon, and Tanabe) were either merger or acquired by competitors or hybrid chemical companies which had already pharmaceutical business unit. Sustaining R&D productivity has become a top priority of pharmaceutical companies. The methodology developed in this dissertation would enable management to monitor changes in R&D productivity relative to the benchmark, understand causes of any dispersion, and consider appropriate measures to resolve issues.

3.4. Summary

This chapter illustrates the importance of focusing on dominant therapeutics and the usefulness of licensing activities, and identified a

possible cause of deterioration of R&D productivity in the Japanese pharmaceutical industry. The study also found that the deterioration of R&D productivity is a possible cause of M&A, albeit there may be other causes. Tools for monitoring R&D productivity within a company and the industry have become more important as the R&D productivity of global pharmaceutical continues to decline. This method will enable management to monitor changes in R&D productivity quantitatively and identify an appropriate R&D strategy.

4. Analysis of global pharmaceutical companies in 2007 and 2012

This chapter attempts to investigate relationships between the R&D productivity for the global pharmaceutical companies and industry consolidations and therapeutic categories, respectively and to visualize the R&D productivity status on individual company basis in 2007 and 2012.

4.1. Results on global pharmaceutical company

This section provides results of R&D productivity and these relationships. First, results from several R&D productivity measurement models are explained. Based on these outcomes, statistical outcomes from relationships between R&D productivity and industry consolidations and therapeutic categories are provided.

4.1.1. Results on R&D productivity

Table 4.1 provides ROI, DEA scores of conventional, separate and R&D Productivity models for the companies in 2007. ROI calculation which was a ratio of accumulated NPV over 5-year accumulated R&D spending illustrates that Biogen had the highest ROI of 187.6% and Ono had the lowest ROI of 17.4%. Based on the conventional DEA analysis, GSK, Biogen, and Shionogi were optimal in R&D productivity. These companies were efficient since they produced relatively high product value effectiveness

given their amount spent on R&D. The separate model indicates that five companies were optimal in cost efficiency and three were optimal in product value. Only GSK remained the most optimal company among the universe. Shionogi was only cost efficient but Biogen were not optimal in either scores. The R&D productivity model also illustrates that GSK was the only company optimal in both cost efficiency and product value effectiveness. Biogen became optimal in cost efficiency but Shionogi remained as cost optimal but not in product value effectiveness. Twelve companies were on the benchmark with regard to cost efficiency. GSK and Merck were on the benchmark with regard to Product value effectiveness. Eleven companies were efficient in terms of drug development but their NMEs were not profitable. Particularly, four of six Japanese companies were the least successful in term of product value effectiveness. Nine companies are found inefficient and ineffective in terms of R&D.

Table 4.1. ROI and R&D productivity scores under several DEA models in 2007

	Ratio Analysis	Conventional DEA	Separate Model		R&D Productivity Model	
	ROI	R&D Productivity	Cost Efficiency Index	Product Value Effectiveness Index	Cost Efficiency Index	Product Value Effectiveness Index
Ono	17.4%	0.997	0.997	45.315	1	45.352
E. Lilly	25.0%	0.197	0.140	2.970	1	5.762
Wyeth	26.3%	0.186	0.176	4.152	1	7.429
DaiichiSankyo	30.6%	0.283	0.549	8.167	1	9.684
Eisai	32.4%	0.399	1	17.516	1	17.516
Schering Plough	34.4%	0.268	0.957	5.976	1	6.042
AstraZeneca	35.9%	0.210	0.236	2.876	1	4.341
Abbott	39.3%	0.263	0.421	4.874	1	6.200
Takeda	40.6%	0.372	0.276	2.486	0.983	3.919
Pfizer	41.0%	0.325	0.176	1.421	0.545	2.012
Roche	43.8%	0.332	0.224	1.699	0.695	2.407
Astellas	44.4%	0.342	0.393	5.053	1	7.109
Shionogi	69.1%	1	1	22.965	1	22.965
Bristol Meyers Squib	69.2%	0.478	0.251	1.812	0.612	2.435
Sanofi	79.5%	0.638	1	1.907	0.419	1.452
Novartis	87.1%	0.736	1	1.498	0.341	1.077
Novo	103.1%	0.603	0.340	1	0.934	3.960
Amgen	110.8%	0.847	0.140	1	0.385	1.521
GSK	112.8%	1	1	1	1	1
Merck	116.0%	0.990	0.421	1	0.421	1
Biogen	187.6%	1	0.846	2.571	1	2.764

Source: Modified from Shimura H., Masuda S., Kimura H [53]

Table 4.2 illustrates comparison between the actual and the optimized number of NMEs in 2007. There were five companies (Eisai, GSK, Merck, Ono, and Shionogi) with the same number of actual and optimized NMEs. Novartis and Sanofi had the higher number of actual NMEs compared with optimized one. This implies that R&D productivity was calculated based on the smaller number of NMEs for both companies. The rest of 14 companies had the lower number of actual NMEs compared with the optimized number and R&D productivity for these companies was calculated based on the number of NMEs which was higher than the actual number.

To illustrate the difference between the separate and RDP model, Amgen is selected as an illustration. Amgen produce five NMEs between 2003 and

2007. When the separate model is considered, Schering Plough and Merck which had the similar amount of R&D spending produced 15 NMEs during the same period, the cost efficiency index of Amgen should be less than 1 or Amgen is not on the efficient frontier. Amgen has the highest product value among companies which produced five NMEs, the product value effectiveness index of Amgen is 1 or Amgen is on the efficient frontier. Thus, Amgen is not efficient in cost efficiency but efficient in product value effectiveness.

Under the RDP model, the results will be different. From the cost efficiency frontier, Amgen needs to produce 15 NMEs to become a benchmark. Assume that Amgen produced 15 NMEs, the product value of Amgen and Pfizer which has the 15 NMEs is compared. Since the product value of Amgen exceeds the one of Pfizer, this is not realistic and it is required to reduce the optimized number of NMEs to lower than 13. The iteration continues until the criterion is met. After several iteration, Amgen's optimized number of NMEs becomes 13. Based on this optimized number of NMEs along with the actual R&D spending and the product values, the cost efficiency and the product value effectiveness indices, and the difference between two indices are calculated.

When the separate and RDP maps are compared, interpretations are different. Based on the separate model, R&D productivity issue of Amgen is

to minimize the R&D spending or increase the number of NMEs while maintaining the current product value. Based on the RDP map, Amgen needs to minimize the R&D spending or increase the number of NMEs at the same time the product value should be improved. In other word, Amgen needs to produce more NMEs which increase the product value.

Table 4.2. Comparison between the actual number of NMEs and the optimized number of NMEs in 2007

Name	# of NMEs		Difference
	Actual	Optimized	
Novo	4	13.0	9.0
Amgen	5	13.0	8.0
Ono	5	5.0	0.0
Shionogi	5	5.0	0.0
E. Lilly	6	23.1	17.1
Takeda	7	17.0	10.0
Wyeth	7	22.2	15.2
Astellas	8	15.5	7.5
Biogen	8	9.4	1.4
BMS	10	17.0	7.0
Abbott	12	18.5	6.5
DaiichiSankyo	12	16.2	4.2
AstraZeneca	13	28.1	15.1
Eisai	13	13.0	0.0
Pfizer	15	29.0	14.0
Roche	15	29.0	14.0
Merck	17	17.0	0.0
Schering Plough	18	18.4	0.4
Sanofi	29	17.0	-12.0
Novartis	32	17.0	-15.0
GSK	33	33.0	0.0

Figure 4.1. Accumulated R&D spending, actual number and optimized number of NMEs of global pharmaceutical companies in 2007

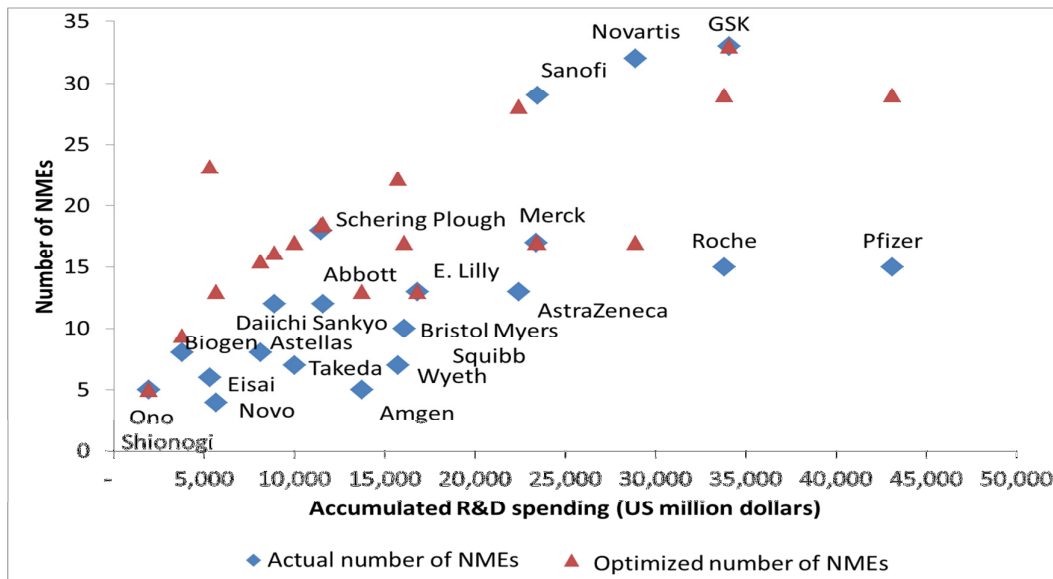
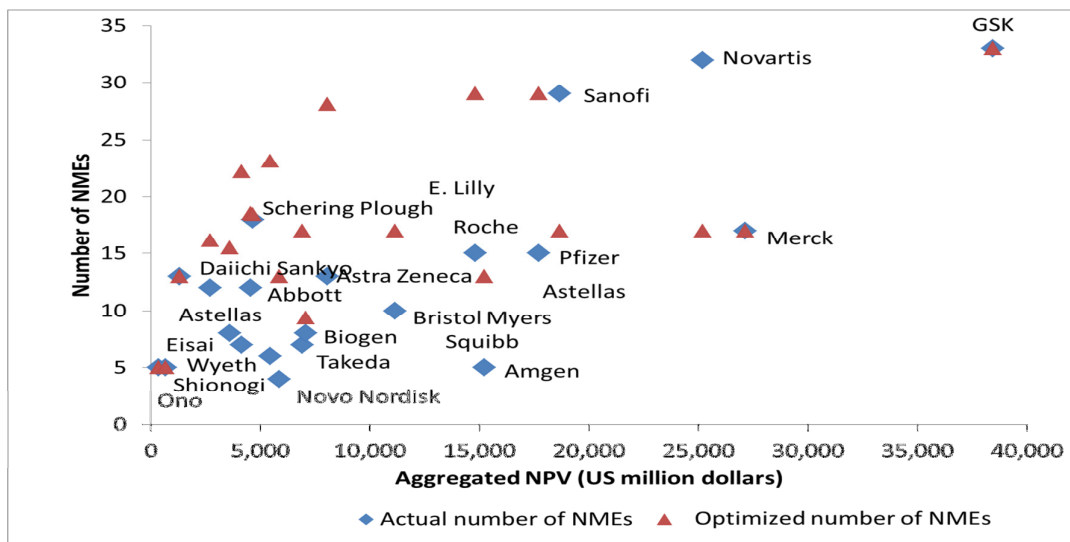


Figure 4.2. Actual number and optimized number of NMEs, accumulated net present value of global pharmaceutical companies in 2007



In 2012, ROI calculation showed that Novo Nordisk had the higher ROI. The conventional DEA model suggests that both Novo and Ono were optimal. There was no company which has both the optimal cost efficiency and

product value effectiveness (Table 4.3). Two companies, Ono and Shionogi, were optimal in cost efficiency while only Novo Nordisk had the optimal product value effectiveness in 2012. The separate model suggests that five companies were optimal in cost efficiency and one is optimal in product value effectiveness. R&D productivity model suggests that two companies were optimal in cost efficiency and one company was optimal in product value effectiveness.

Table 4.3. ROI and R&D productivity scores under three DEA models in 2012

	Ratio Analysis	Conventional DEA	Separate Model		R&D Productivity Model	
	ROI	R&D Productivity	Cost Efficiency Index	Product Value Effectiveness Index	Cost Efficiency Index	Product Value Effectiveness Index
Abbott	9.8%	0.148	0.130	2.497	0.158	15.769
Sanofi	13.7%	0.096	0.168	5.617	0.079	5.617
Roche	16.7%	0.085	0.071	3.250	0.056	3.250
Pfizer	17.8%	0.082	0.219	2.639	0.048	2.639
Lilly	19.0%	0.138	0.280	5.958	0.116	5.958
Ono	20.0%	1	1	9.439	1	9.439
Shionogi	21.9%	0.833	1	44.543	1	44.543
DaiichiSankyo	22.2%	0.266	0.728	11.853	0.270	11.853
AstraZeneca	23.7%	0.135	0.098	4.037	0.098	4.037
Amgen	25.4%	0.192	0.135	1	0.164	6.314
Merck	26.7%	0.112	1	2.101	0.057	2.101
Biogen	29.7%	0.413	0.357	2.264	0.435	14.293
Astellas	33.2%	0.300	0.751	8.193	0.278	8.193
Novartis	37.1%	0.142	0.099	1.657	0.063	1.657
Takeda	46.2%	0.251	1	3.676	0.174	3.676
GSK	57.0%	0.204	0.297	1.348	0.079	1.348
BMS	70.6%	0.286	0.258	1.933	0.140	1.933
Eisai	72.3%	0.443	1	4.535	0.336	4.535
Novo	302.5%	1	0.310	1	0.310	1

Table 4.4 illustrates comparison between the actual number of NMEs and the optimized number of NMEs for individual company in 2012. There were four companies (Biogen, Novo Nordisk, Ono, and Shionogi) with the same number of actual and optimized number of NMEs. Abbott, Amgen, and Biogen had the higher number of actual NMEs compared with optimized

number. This implies that R&D productivity was calculated based on the smaller number of NMEs for both companies. The rest of 12 companies had the lower number of actual NMEs compared with the optimized number and R&D productivity for these companies was calculated based on the number of NMEs which was higher than the actual number.

Table 4.4. Comparison between the actual number of NMEs and the optimized number of NMEs in 2012

Name	# of NMEs		Difference
	Actual	Optimized	
Abbott	3	4.0	1
Amgen	3	4.0	1
Biogen	3	4.0	1
Ono	3	3.0	0
AstraZeneca	4	4.0	0
Novo	4	4.0	0
Shionogi	4	4.0	0
Roche	5	4.0	-1
Novartis	6	4.0	-2
BMS	7	4.0	-3
Sanofi	8	4.0	-4
Lilly	9	4.0	-5
Astellas	10	4.0	-6
DaiichiSankyo	10	4.0	-6
Eisai	11	4.0	-7
GSK	13	4.0	-9
Pfizer	15	4.0	-11
Takeda	18	4.0	-14
Merck	20	4.0	-16

Figure 4.3. Accumulated R&D spending, actual number and optimized number of NMEs of global pharmaceutical companies in 2012

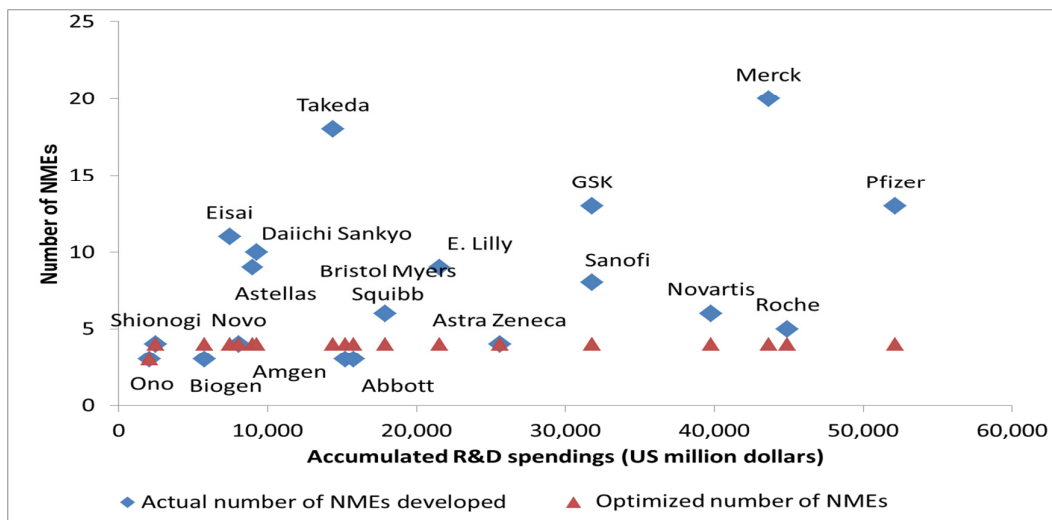
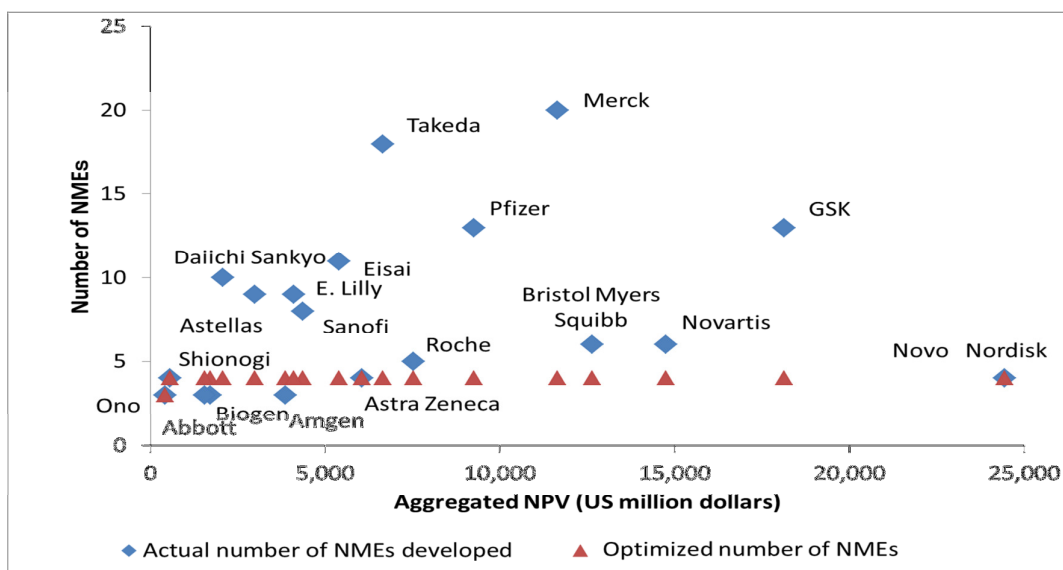


Figure 4.4. Actual number and optimized number of NMEs, accumulated net present value of global pharmaceutical companies in 2012



4.1.2. Results on relationships between R&D productivity and industry consolidations

Table 4.5 demonstrated a significant association between cost efficiency and

the number of M&A activities a company engages in ($p = 0.022$) and M&A transaction amounts ($p = 0.05$).

Table 4.5. Statistical results on R&D productivity scores and industry consolidations

		R&D Efficiency	R&D Effectiveness	R&D Productivity
M&A Amount	P-Value	0.022**	0.193	0.191
	t-Stat	-2.511	1.356	-1.363
# of M&A transactions	P-Value	0.030**	0.304	0.300
	t-Stat	-2.363	1.059	-1.069

Source: Shimura H., Masuda S., Kimura H [5]

4.1.3. Results on relationships between R&D productivity and therapeutic categories

Table 4.6 illustrates statistical results based on Man-Whitney U test. In 2007, there is a difference in product value effectiveness for all five categories between the scores of the two groups for all five categories (p -value < 0.001). Companies which involved in all franchise except CNS had a better score on product value effectiveness index (p -value < 0.001). Companies who developed CNS had lower product value while companies who developed the rest of categories had higher product value. There is a difference in cost efficiency between the scores of two groups for developing vaccine (p -value < 0.005) in 2007. Or companies who developed vaccine had lower cost efficiency. An examination of the averages of each component of R&D productivity and therapeutic categories in 2007 demonstrates that the companies which involved in four therapeutic categories were relatively

optimal in product value effectiveness but companies which involved in CNS were relatively less optimal in product value effectiveness. Companies which involved in vaccine were relatively less optimal in cost since the company's DEA scores becomes 1 when they achieves the efficiency level.

Table 4.6. Mann-Whitney U test results on five major therapeutic category and R&D productivity components in 2007

Therapeutic category		n	Cost Efficiency Index			Product Value Effectiveness		
			Average	Z-Score	p-value	Average	Z-Score	p-value
Cancer	Developed	13	0.724	0.711	0.477	5.096	5.349	<0.001***
	Not-developed	8	0.990			11.212		
Cardiovascular	Developed	15	0.801	0.118	0.906	2.914	5.345	<0.001***
	Not-developed	6	0.887			6.795		
CNS	Developed	15	0.827	0.711	0.477	7.828	5.349	<0.001***
	Not-developed	6	0.822			5.259		
Diabetes	Developed	13	0.790	0.118	0.906	5.929	5.345	<0.001***
	Not-developed	8	0.883			7.920		
Vaccine	Developed	7	0.740	3.100	0.002***	3.214	5.488	<0.001***
	Not-developed	14	0.868			9.532		

In 2012, there is a difference in product value effectiveness for all five categories between the scores of the two groups for all five categories (p-value <0.001) but there is a difference in cost efficiency for between the scores of the two groups for developing cancer (p-value <0.01) and respiratory (p-value <0.001) categories. An examination of the averages of each component of R&D productivity and therapeutic categories in 2007 demonstrates that the companies which involved in all five therapeutic categories were relatively optimal in product value effectiveness. Companies which involved in cancer and respiratory were relatively less optimal in cost since the company's DEA score becomes 1 when they achieves the efficiency level.

Table 4.7. Mann-Whitney U test results on five major therapeutic category and R&D productivity components in 2012

Therapeutic category		n	Cost Efficiency Index			Product Value Effectiveness		
			Average	Z-Score	p-value	Average	Z-Score	p-value
Cancer	Developed	15	0.164	2.724	0.006***	5.942	5.238	<0.001***
	Not-developed	4	0.602			14.755		
Cardiovascular	Developed	9	0.236	0.537	0.591	5.568	5.219	<0.001***
	Not-developed	10	0.274			7.239		
CNS	Developed	11	0.226	0.509	0.611	3.715	5.201	<0.001***
	Not-developed	8	0.297			9.297		
Diabetes	Developed	9	0.254	0.537	0.591	3.205	5.219	<0.001***
	Not-developed	10	0.257			7.815		
Respiratory	Developed	3	0.066	3.828	<0.001***	1.702	5.420	<0.001***
	Not-developed	16	0.291			8.941		

4.1.4. Results on RDP map

Figure 4.5 and Figure 4.6 depict the separate and RDP map for global pharmaceutical companies in 2007, respectively. In 2007, based on efficiency/inefficiency in cost efficiency and product value effectiveness, each company was classified into four groups. GSK on the upper right corner of the RDP map was efficient in both the cost efficiency and the product value effectiveness, or was a benchmark in 2007. Merck was on the left upper side of the map and they were inefficient in the cost efficiency process but efficient in the product value effectiveness. 11 out of 21 companies were efficient in the cost efficiency but inefficient in the product value effectiveness. Finally, nine out of 21 were both inefficient in the cost efficiency and product value effectiveness.

Figure 4.5. Separate R&D productivity map of global pharmaceutical industry in 2007

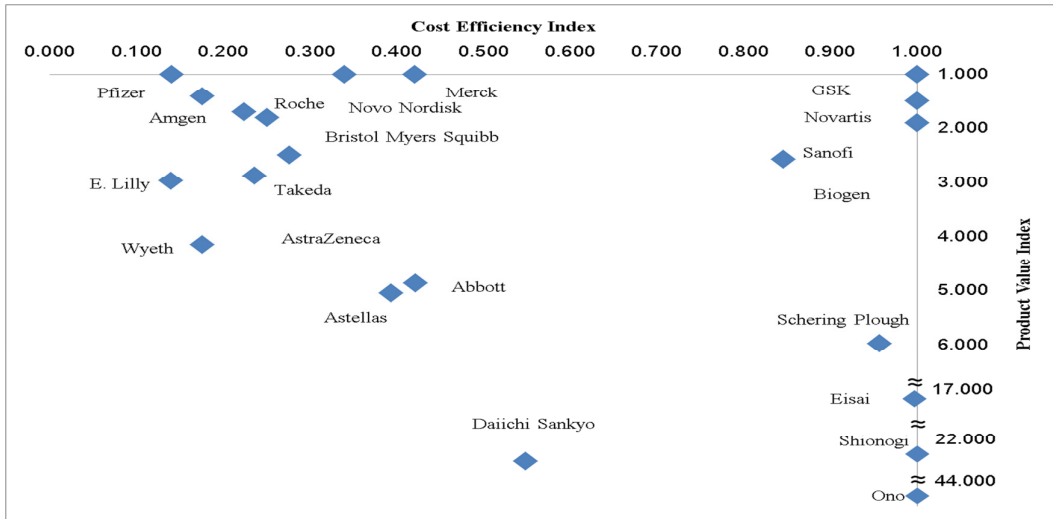
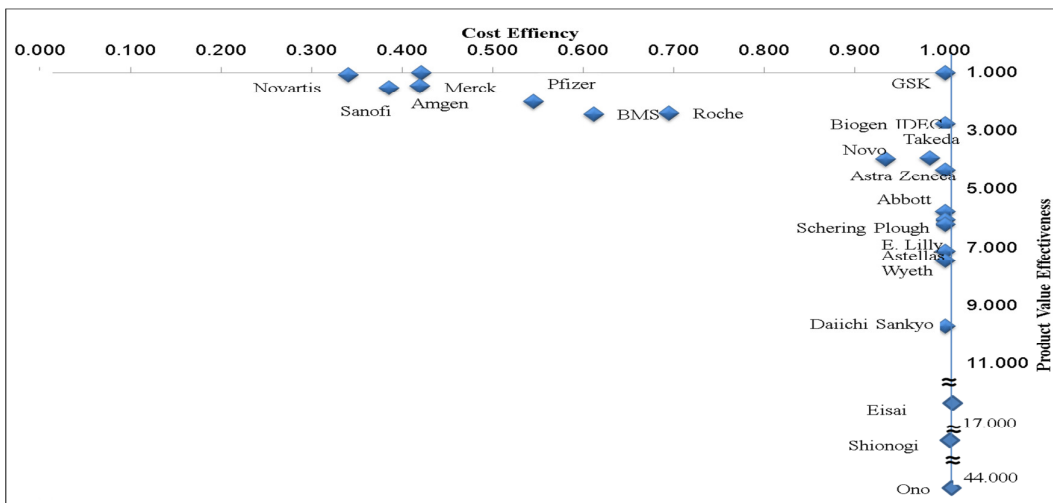


Figure 4.6. RDP map of global pharmaceutical industry in 2007



Source: Shimura H., Masuda S., Kimura H [53]

Figure 4.7 and Figure 4.8 depict the separate R&D productivity and RDP maps for global pharmaceutical companies in 2012, respectively. In 2012, majority of companies were relatively low cost efficient but high product

value effectiveness. Both Ono and Shionogi were relatively high cost efficient but low product value effectiveness. Furthermore, based on efficiency/inefficiency in cost efficiency and product value effectiveness, each company was classified into three groups, instead of four groups in 2012. No company was on the upper right corner of the RDP map or no company was a benchmark in 2012. Novo Nordisk was on the left upper side of the map and they were inefficient in the cost efficiency process but efficient in the product value effectiveness. 16 out of 21 companies were both inefficient in the cost efficiency and product value effectiveness.

Figure 4.7. Separate R&D productivity map of global pharmaceutical industry in 2012

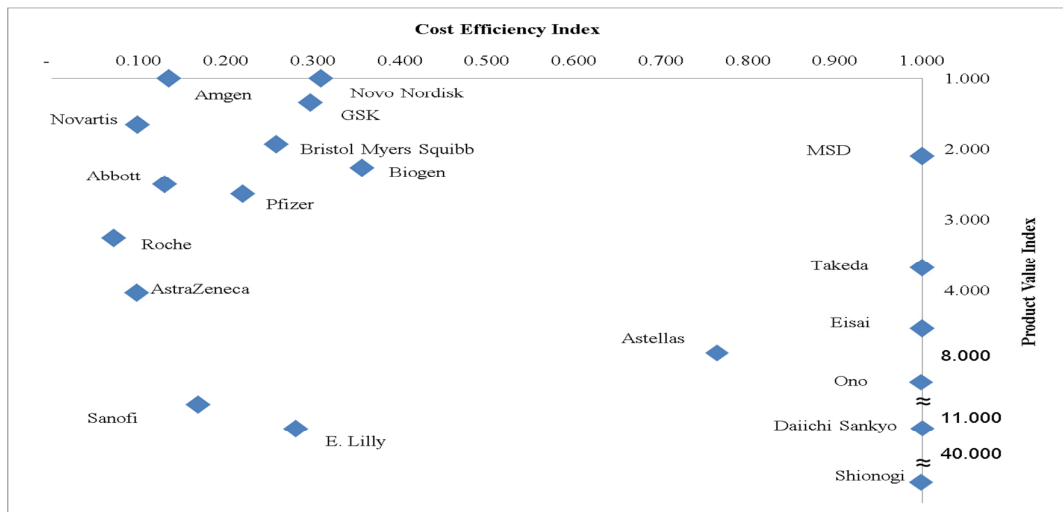
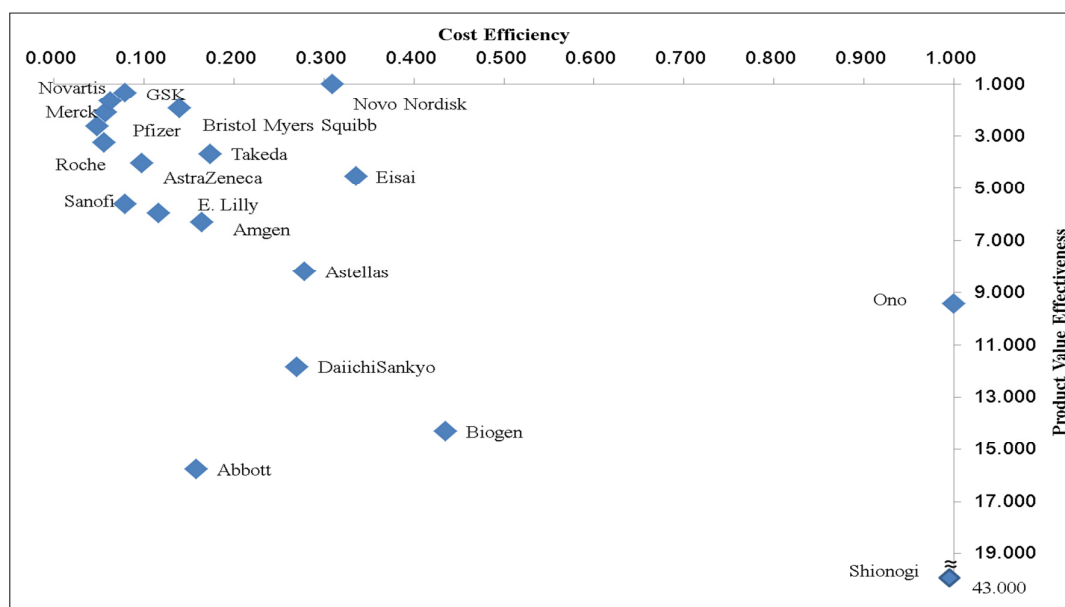


Figure 4.8. RDP map of global pharmaceutical industry in 2012



4.2. Discussions on R&D productivity among global pharmaceutical industry

The R&D productivity model illustrates the R&D productivity issues which a company faces in that time period. Even though there may not be casual relationships, the RDP map enables to visualize the current status among peers and to foresee the corporate behaviors in order to either sustain or improve the R&D productivity.

4.2.1. Discussions on R&D productivity

Table 4.6 shows comparison between scores from the R&D productivity model in 2007 and 2012. The table shows that the most of companies were cost inefficient and a lack of cost efficiency is an industry issue in 2012. Note that Pfizer which acquired Wyeth has moved down its rank in the cost

efficiency scores from 17th to 19th; however, this result only indicated the R&D cost efficiency of Pfizer was ranked lower among peers in 2012 and this does not indicate the failure of Wyeth acquisition since other factors should be considered.

Table 4.8. R&D productivity ranking in 2007 and 2012

	2007				2012			
	Cost Efficiency		Product Value		Cost Efficiency		Product Value	
	Ranking	Efficiency	Ranking	Efficiency	Ranking	Efficiency	Ranking	Efficiency
GSK	1	1	1	1	14	0.079	2	1.348
Biogen	1	1	9	2.764	2	0.435	17	14.293
AstraZeneca	1	1	12	4.341	12	0.098	9	4.037
E. Lilly	1	1	13	5.762	11	0.116	12	5.958
Schering Plough	1	1	14	6.042	-			
Abbott	1	1	15	6.200	9	0.158	18	15.769
Astellas	1	1	16	7.109	5	0.278	14	8.193
Wyeth	1	1	17	7.429	-			
DaiichiSankyo	1	1	18	9.684	6	0.270	16	11.853
Eisai	1	1	19	17.516	3	0.336	10	4.535
Shionogi	1	1	20	22.965	1	1	19	44.543
Ono	1	1	21	45.352	1	1	15	9.439
Takeda	13	0.983	10	3.919	7	0.174	8	3.676
Novo	14	0.934	11	3.960	4	0.310	1	1
Roche	15	0.695	7	2.407	17	0.056	7	3.250
BMS	16	0.612	8	2.435	10	0.140	4	1.933
Pfizer	17	0.545	6	2.012	18	0.048	6	2.639
Merck	18	0.421	1	1	16	0.057	5	2.101
Sanofi	19	0.419	4	1.452	13	0.079	11	5.617
Amgen	20	0.385	5	1.521	8	0.164	13	6.314
Novartis	21	0.341	3	1.077	15	0.063	3	1.657

An introduction of the optimized number of NMEs may dilute the product value effectiveness index but provides more focused R&D productivity strategy. To illustrate how the intermediary works, two cases are considered: the actual number of NMEs is less than the optimized one and the actual number of NMEs is higher than the optimized one. Amgen produced 5 NMEs between 2002 and 2007 and had the product value of

15,226 million dollars in 2007. Since the separate model produces the cost efficiency index is less than 1, it suggests Amgen needed to reduce the R&D spending or produce more NMEs since comparators produce more NMEs. The separate model produced product value effectiveness index of 1: thus, the company is on the benchmark. The management decision would be either to reduce the R&D cost or produce more NMEs regardless of its potential profits. When the optimized number is employed, the management decision will be different. Based on the cost efficiency efficient frontier, comparators (Merck and Schering Plough) produced 15 NMEs; thus, Amgen is not optimal in cost efficiency. If Amgen uses 15 NMEs as the optimized number of NMEs, Amgen's product value is compared with the product value of Pfizer of 15 NMEs. Since the Amgen's product value did not exceed the product value of Pfizer (21,839 million dollars), Amgen was able to have 15 NMEs under the current constraints but an objective of the map is minimize the difference between cost efficiency and product value indices. After several iterations to find the optimal R&D productivity, the optimized number of NMEs was 13, which leads to the cost efficiency index of 0.164 and the product value effectiveness of 6.314. This suggests that Amgen has inherent risk of reliance on relatively a few number of NMEs but their product values were now not on the benchmark. These results suggested that Amgen needed to improve both of cost efficiency and produce value

effectiveness and Amgen needed more NMEs which contribute to the higher product value so that an increase of NMEs does not dilute the overall R&D product value.

The latter case is that the optimized number of NMEs was less than the actual number of NMEs. Novartis produced 32 NMEs between 2002 and 2007 and its product value was 25,185 million dollars. By using the separate model, Novartis is optimal in cost efficiency since comparators produced less. On the other hand, since Merck with 17 NMEs had the net present value of 27,122 billion dollars in product value, Novartis had much smaller product value with 33 NMEs. Novartis is optimal in cost efficiency but not in product values. The management decision would be to increase the product value. When the R&D Productivity model is employed, the management decision will be different. After several iterations, their optimized number of NMEs became 17 and the model provided the cost efficiency index of 0.063 and the product value effectiveness of 1.657. This suggests that Novartis needs to focus on smaller number of NMEs (i.e., reduce the number of NMEs from 33 to 17) in order to improve the current product value and achieve the optimal R&D productivity. At the same time, Novartis needs to improve their product value such as seeking additional indications.

4.2.2. Discussions on relationships between R&D productivity and industry consolidations

Analyses revealed at least two interesting outcomes. First, 10 companies lacked the ability to efficiently develop NMEs. As a result, nine of them acquired at least one company between 2008 and 2012. These nine transactions were collectively worth 251 billion dollars, which represented 64% of the total value of all M&A transactions in that time period. This suggests that to effectively compensate for their lack of cost efficiency, acquisitions represent one solution for getting drugs in the pipeline. In addition, the nine companies that engaged in M&A activities were responsible for seven of the top 10 most valuable M&A transactions between 2008 and 2012. Second, 11 companies had cost efficiency but lacked profitable NMEs. Analysis suggests that Wyeth, Schering-Plough, and Abbott represented the three least-productive companies in the US in terms of R&D. Later, Pfizer, whose cost efficiency and product value effectiveness were substandard, acquired Wyeth. Merck, which was only successful in terms of product value effectiveness, acquired Schering-Plough. In 2012, Abbott, the second-least cost effective company in terms of R&D, announced its intention to divide into two separate entities. One of these entities was to focus on the development of novel drugs; the other was to perpetuate the company's existing business. These observations reinforced findings

generated by LaMattina [17] that suggested that to achieve top-line growth without an appropriate R&D strategy or improvement in R&D productivity, many companies will opt to engage in M&A activities in the near future. Results further indicated that companies with lower cost efficiency scores (i.e., cost-inefficient drug developers) were more likely to actively engage in M&A activities.

4.2.3. Discussions on relationships between R&D productivity and therapeutic categories

Companies involved in vaccine in 2007, cancer and respiratory in 2012 were relatively cost inefficient. For the companies developed in cancer drugs, there was no statistically significance was found in 2007 but found in 2012. A possible reason that a deterioration of cost efficiency for cancer drugs is that the number of non-cancer drug developers decreased from 8 to 4 companies between 2007 and 2012, resulting in intense competition to increase the R&D cost such as recruiting patients. There were 15 biological NMEs including antibody, protein, and vaccine out of 44 cancer related NMEs in 2007 and 14 biological NMEs out of 37 cancer related NMEs in 2012. Although there is no information on R&D spending for cancer related NMEs, a shifting toward to biological drug development concentration might have worsened the cost efficiency of the pharmaceutical industry.

Table 4.9. Cancer drugs under development by therapeutic modality

Small molecule		Biologic and others	
2007	2012	2007	2012
5FU+enzyme inhibitor	axitinib	bevacizumab	ado-trastuzumab emtansine
axitinib	bosutinib	denosumab	brentuximab Vedotin
cabazitaxel	brivanib	ipilimumab	elotuzumab
calcitriol	crizotinib	lumiliximab	farletuzumab
cediranib	dabrafenib	ocrelizumab	galiximab
dasatinib	dacomitinib	ofatumumab	ipilimumab
elesclomol	enzalutamide	panitumumab	necitumumab
eltrombopag	enzastaurin	pertuzumab	ofatumumab
enzastaurin	eribulin mesylate	Rituximab	pertuzumab
eribulin mesylate	everolimus	tremelimumab	ramucirumab
erlotinib	iniparib	aflibercept	aflibercept
everolimus	lapatinib	romiplostim	trebananib
flavopiridol	linifanib	astuprotimut-R	talimogene laherparepvec
imatinib	midostaurin	tecemotide	degarelix
ixabepilone	motesanib	MVA-5T4	
lapatinib	ombrabulin		
larotaxel	orterone		
lonafarnib	pasireotide		
nelarabine	ridaforolimus		
nilotinib	tivantinib		
pasireotide	trametinib		
patupilone	vandetanib		
pazopanib	vemurafenib		
ridaforolimus			
sunitinib			
vandetanib			
vinblastine			
xaliproden			
zibotentan			

Findings indicate that there is a therapeutic category which may dilute the cost efficiency. While there is no proven causal relationship between the inefficient therapeutic category and deterioration of R&D productivity, at least two interesting phenomena were observed. All companies (excluding Wyeth) involved in vaccine development in 2007 (including GSK, AstraZeneca, and Abbott) that were cost efficient in 2007, were cost inefficient in 2012. Another interesting observation is that companies that developed cancer drugs in 2012 engaged in business reengineering after 2013. Based on press releases, 11 out of the 19 companies (Merck,

AstraZeneca, Novartis, Takeda, E. Lilly, Roche, Sanofi, Astellas, Eisai, Pfizer, and Bristol Myers-Squibb) in the industry announced significant employee layoffs between 2012 and 2014. Pfizer separated its animal healthcare business in 2013 and Merck announced a plan to sell its animal health and consumer products businesses in January 2014. AstraZeneca announced it acquired Bristol-Myers Squibb's entire interest in the companies' diabetes alliance in February 2014. Novartis acquired GSK's cancer drug business for 16 billion dollars, sold its vaccines division (excluding the influenza business) to GSK for 7.1 billion dollars, and combined its consumer health care units.

Analyzing relationships between R&D productivity and therapeutic categories implies that there is an evidence of a possible link between certain therapeutic categories and cost efficiency. However, results do not discourage a company to invest in cost inefficient therapeutic category and rather emphasizes on a balance between cost efficiency and product value effectiveness along with other valuation tools when selecting therapeutic category selection. Even though therapeutic category selection and prioritization criteria may vary among companies, the RDP map allows management to examine current R&D productivity for further improvement. Otherwise, the inherent risk of dropping an NME due to adverse events can be magnified. Thus, a company must seek an appropriate balance between

cost efficiency and product value effectiveness to maximize R&D productivity. However, the study does not discourage companies to invest in cost inefficient therapeutic categories, but rather it emphasizes a balance between cost efficiency and product value effectiveness along with other valuation tools when selecting therapeutic categories.

4.3. Summary

This study focuses and evaluates on the R&D productivity of 21 global pharmaceutical companies from 2002 to 2007 and from 2007 to 2012. Results could be varied utilizing a different approach and these findings proved that the R&D productivity model is the most useful model. This chapter also illustrated the cost efficiency was a key determinant for the M&A, albeit there may be other causes. As we have seen in a Japanese case, therapeutic selection is an important element of the company's R&D strategy and a balance between cost efficiency and product value effectiveness should be considered; otherwise, a concentration on a few numbers of NMEs imposes the company hardships. Based on the RDP map in 2012, the pharmaceutical industry faces a lack of cost efficiency and indicates that alternative ways to improve the R&D productivity must be sought.

5. Discussions/Conclusion

This chapter discusses findings from Japanese and global pharmaceutical cases. Based on results from the RDP map and relationships between R&D productivity, industry consolidation, and therapeutic categories, three options to improve overall R&D strategy are discussed. At the end, future research topics are suggested and limitations of this dissertation are discussed.

5.1. Discussions on R&D productivity

There are many approaches to evaluate R&D productivity; however, few consider pharmaceutical industry characteristics such as the relationship between R&D spending and number of NMEs, and risk/return profiles of therapeutic categories. The R&D productivity model incorporates the uniqueness of pharmaceutical R&D productivity and displays individual company's relative R&D productivity and position within the pharmaceutical industry. This unique approach also enables management to pinpoint strengths and weaknesses of the current R&D strategy and identify potential solutions.

The most important reason to deconstruct R&D productivity into two factors is to identify the inherent risk of relying on a small number of NMEs regarding product values. Since cost efficiency represents how a company

efficiently produces an NME given R&D spending, a company with relatively less-optimal cost efficiency is considered highly dependent on a few number of NMEs for product value. To improve overall R&D productivity, the company can consider at least three options: first, reduce R&D spending. Second, focus on appropriate therapeutic categories. In both the Japanese and global industries, there are therapeutic categories that relate to the companies' cost inefficiency that selected the categories. In 2014, GSK and Novartis announced a business swap: GSK traded their cancer business to Novartis for Novartis's vaccine business. The third option is to pursue M&A, as has been observed several times in both the Japanese and global pharmaceutical industries. This important topic will be deeply discussed later in this chapter.

Companies with relatively less-optimal product value effectiveness should seek business strategies to maximize product value because product value effectiveness measures how companies effectively increase product value given a number of NMEs produced relative to the industry benchmark. There are several approaches to maximize product value, such as expanding indications, regional coverage, and licensing. Cases in which the company sought licensing transactions with Japanese pharmaceutical companies are observed. Shionogi and Tanabe, which were optimal in cost efficiency but not optimal in product value effectiveness, licensed out products that are

well known today. In 2004, Ono, another Japanese company in the same category, launched its diabetic drug, Sitagliptin (originally developed by Merck), in exchange for licensing a drug for chemotherapy-induced nausea and vomiting. Abbott Laboratories, which had less-optimal cost efficiency and product value effectiveness, spun off its proprietary pharmaceutical business as Abbvie in 2013.

Seven out of 21 companies were not optimal in cost efficiency in 2007, but 7 out of 19 companies were not optimal in cost efficiency in 2012. This implies cost efficiency improvement could be an industry issue today. This phenomenon may be partially explained by the decline in the number of NMEs marketed, filed, or undergoing P-III trials while R&D spending increased. In 2007, the industry spent 340.3 billion dollars and produced 274 NMEs, but spent 298.6 billion dollars and produced 152 NMEs in 2012. While another conventional method could imply the same findings, the RDP map enables visualization of an individual company's R&D status and identifies their relative productivity among peers. Because scores from the RDP map are calculated based on two-stage DEA, they represent the company's optimal R&D productivity. Thus, the map visualizes strengths and weaknesses of the company and provides possible solutions to improve R&D productivity.

5.2. Discussions on relationships between R&D productivity and industry

consolidations

Based on the Malmquist index, R&D deterioration among Japanese companies shows that companies with high MI scores (i.e., their R&D productivity declined relatively significant) were likely to merge within a few years, though no statistical testing was conducted. From the RDP maps, companies with less-optimal product value effectiveness and companies with optimal cost efficiency tended to pursue M&A. Chugai, which was least optimal in cost efficiency, was acquired by Roche. Toyama Chemical, which had the second lowest product value effectiveness score, and Yoshitomi, which had the third lowest product value effectiveness score, merged after 1998. Industry consolidation in 2003 and 2006 has similar characteristics. However, M&A is not always an appropriate solution because the best fit may not be available at the time of decision making. A company may be able to sustain its R&D productivity by either licensing or by eliminating non-core businesses. For example, Shionogi, which was the least optimal in product value effectiveness, licensed several antibiotics during the 1990s and licensed Rosuvastatin to AstraZeneca. Eisai, which had the second lowest cost efficiency score, made a strategic alliance with Pfizer in 1994 regarding the Alzheimer's drug, Donepezil. These events are supported by Danzon et al. [28] who find that licensing products tended to increase the probability of success, particularly if the licensee was a large firm. Shionogi

also sold its wholesale business unit in 1998. Fujisawa (fourth worst MI score), withdrew its generic drug business in the US in 1998.

Analyses regarding the global pharmaceutical industry reveal at least two interesting outcomes. First, 10 companies lacked the ability to efficiently develop NMEs and as a result, nine of them acquired at least one company between 2008 and 2012. These nine transactions were collectively worth 251 billion dollars, representing 64% of the total value of all M&A transactions during that time period. This suggests that to effectively compensate for lack of cost efficiency, acquisitions represent one solution for getting drugs into the pipeline. In addition, the nine companies that engaged in M&A were responsible for seven of the 10 largest M&A transactions between 2008 and 2012. Second, 11 companies had optimal cost efficiency but lacked profitable NMEs. Analysis suggests Wyeth, Schering-Plough, and Abbott represented the three least-productive companies in the US in terms of R&D. Later, Pfizer, whose cost efficiency and product value effectiveness were substandard, acquired Wyeth. Merck, which was only successful in terms of product value effectiveness, acquired Schering-Plough. In 2012, Abbott, the second least cost effective company in terms of R&D, announced its intention to separate into two entities; one was to focus on the development of novel drugs and the other was to perpetuate the company's existing business. These observations reinforce LaMattina's findings [17],

that to achieve top line growth without an appropriate R&D strategy, or improve R&D productivity, many companies will pursue M&A in the near future. Results further indicate companies with lower cost efficiency scores (i.e., cost-inefficient drug developers) are more likely to actively pursue M&A. As mentioned earlier, a series of business realignments such as spinning off non-core businesses are observed instead of industry consolidation among peers.

5.3. Discussions on relationships between the R&D productivity and therapeutic categories

Analyzing relationships between R&D productivity and therapeutic categories implies there is evidence of a possible link between R&D productivity, particularly cost efficiency, and certain therapeutic categories. Based on relationships between R&D productivity and therapeutic categories, therapeutic category selection can be a crucial factor for improving R&D productivity.

Among Japanese companies from 1980 to 1997, R&D productivity of companies that developed antibiotics (a dominant category) deteriorated less. The deterioration of R&D productivity has been a major issue in the Japanese pharmaceutical industry and involvement in antibiotics R&D helped sustain R&D productivity of Japanese pharmaceutical companies during the 1980s. Further, based on the RDP map, companies involved in

lifestyle disease drug development had less optimal cost efficiency and no other therapeutic categories show a similar result. However, companies with lifestyle disease drugs in their product portfolio were more optimal regarding product value effectiveness versus companies without the drugs. The difference is clearly bigger than in the other three categories. While no causal relationship was investigated, companies heavily involved in lifestyle diseases increased their reliance on product values that had a small number of NMEs, and gained significant product value effectiveness.

Similar findings are observed among global pharmaceutical companies. While there is no proven causal relationship between the inefficient therapeutic category and deterioration of R&D productivity, at least two interesting phenomena were observed. All companies (excluding Wyeth) involved in vaccine development in 2007 (including GSK, AstraZeneca, and Abbott) that were cost efficient in 2007, were cost inefficient in 2012. Another interesting observation is that companies that developed cancer drugs in 2012 engaged in business reengineering after 2013. Based on press releases, 11 out of the 19 companies in the industry announced significant employee layoffs between 2012 and 2014. Pfizer separated its animal healthcare business in 2013 and Merck announced a plan to sell its animal health and consumer products businesses in January 2014. AstraZeneca announced it acquired Bristol-Myers Squibb's entire interest in the

companies' diabetes alliance in February 2014. Novartis acquired GSK's cancer drug business for 16 billion dollars, sold its vaccines division (excluding the influenza business) to GSK for 7.1 billion dollars, and combined its consumer health care units.

Even though therapeutic category selection and prioritization criteria may vary among companies, the RDP map allows management to examine current R&D productivity for further improvement. Otherwise, the inherent risk of dropping an NME due to adverse events can be magnified. Thus, a company must seek an appropriate balance between cost efficiency and product value effectiveness to maximize R&D productivity. However, the study does not discourage companies to invest in cost inefficient therapeutic categories, but rather it emphasizes a balance between cost efficiency and product value effectiveness along with other valuation tools when selecting therapeutic categories.

Based on analyses of R&D productivity among pharmaceutical companies, two alternatives are considered to sustain R&D productivity over the long term. First, companies should focus on dominant therapeutic franchises and balance cost efficiency and product value effectiveness. Regarding both the Japanese and global cases, therapeutic category selection is a crucial part of the decision making process for pharmaceutical companies. As scientific innovation has progressed, several therapeutic categories have emerged

such as lifestyle diseases and oncology. At the same time, a balance between cost efficiency and product value effectiveness has possibly been sacrificed. Examples include antibiotics development during the 1980s and lifestyle diseases during the 1990s in Japan, vaccine in 2007, and cancer and respiratory in 2012 in the global pharmaceutical industry. The imbalance of these factors has led to industry consolidation because company earnings sustainability is in jeopardy.

Second, if a company becomes less optimal or fails significantly to catch up with the benchmark, pursuing M&A may no longer be a solution. In this dissertation, the RDP map projected from global pharmaceutical companies' status in 2012 was provided. The majority of the companies lack cost efficiency. This leads to relying on cost cutting to sustain current economies of scale. As a company seeks economies of scale and becomes successful, R&D spending is increased and the sustainability issue arises. The company has at least three options: 1) devote to potentially high value products with high failure risk, 2) diversify the therapeutic categories, and 3) collaboration. If companies select the first option, inherent risks from relying on limited numbers of NMEs will be increased.

The second option seems to be a solution but appropriate resource allocation among therapeutic categories will be another issue, such as expertise and timing of the product launch. The RDP map in 2012 shows that several

companies (i.e., Abbott) have sought alternative ways to improve overall R&D productivity. Some chose to spin off non-core businesses to focus on the core business, and some chose to abandon non-core therapeutic categories and focus on core therapeutic categories. Since most companies need NMEs to balance R&D productivity, several acquisitions regarding small bio-ventures or specialty pharmaceutical companies will continue. This might be a solution for the short term but not necessarily for the long term.

The final option will be partnerships with academia or other institutions. Budgets for both pharmaceutical companies and academic research centers have become tighter, and due to earnings shortfalls, some pharmaceutical companies closed their research centers. Thus, partnerships will be vital to create therapeutic breakthroughs and some pharmaceutical companies have already initiated this approach. There are successful examples of discoveries from academic labs coming to the market. For example, Merck enjoyed at least two vaccine products that originated from academic laboratories: RotaTeq and Gardasil. While there has been continuing potential tensions between industry and academia, such as publication and patent strategies and related conflicts of interest, the need for partnerships to solve unmet medical needs and healthcare issues is inevitable.

5.4. Further research topics

This dissertation focuses on pharmaceutical companies' R&D productivity;

to measure overall R&D productivity, an extended model should be considered. In this thesis, the RDP map is constructed with variables such as the accumulated R&D spending, the number of NMEs, NPV, sales and operating profits as the product value. In order to measure overall R&D productivity, factors including infrastructure of the company (i.e., the number of researchers), therapeutic specific risks, the portfolio value of existing products must be incorporated. As the size of a company increases, management considers another driver of earnings besides R&D productivity, marketing, and sales, to sustain earnings levels in both the short and long term.

Since this dissertation employs data from large, publicly listed pharmaceutical companies, an extended model incorporating smaller bio companies should be considered in order to generalize R&D productivity of the pharmaceutical industry. As mentioned earlier, the pharmaceutical industry faces the cost efficiency issue and can develop NMEs to cover the expenses. To visualize the bio pharmaceutical industry, as a whole, smaller companies with niche therapeutic categories should be included to verify that the pharmaceutical industry indeed faces the R&D productivity issue.

Selecting product value is an important process when measuring the product value effectiveness index. For global pharmaceutical industry, the product value effectiveness index depends solely on product value of NMEs

after phase III trials due to variability of level of R&D information disclosure. If the complete data set of phase II trials is obtained, more practical R&D productivity can be measured. When R&D productivity of global pharmaceutical companies, product value of NMEs after phase III are employed but a relationship with existing products are not considered. By relating the existing products and the current therapeutic categories under development, a level of complementation between the RDP map and existing product portfolio can be quantified.

There are many factors besides the R&D productivity to impact on the industry consolidation. Specially, the patent expiry of the large products has been considered as a key factor on the industry consolidation; however, this research does not compare the existing products and NMEs under consideration. Incorporating the remaining time left to the patent expiry can enhance the usability of the RDP map.

While relationships between therapeutic categories and R&D productivity were found statistically significant, no casual relationships between them were examined. Thus, it is difficult to make a decision on therapeutic selection solely from outcomes from the RDP maps. The current RDP map remains as a tool to visualize the current R&D productivity issues by company and further development is needed to use as a more effective decision making tool to evaluate R&D productivity by therapeutic category

on a multidimensional level with the same framework. This approach is feasible if internal data for ongoing R&D programs for each therapeutic franchise can be obtained. In this way, it is possible to monitor changes in R&D productivity within a company by using the NPV of each NME by therapeutic class. Furthermore, adding factors including therapeutic specific risks, competition, and a barrier to entry can enhance the RDP map approach as a better decision making tool.

While this thesis identifies relationships between industry consolidation and R&D productivity, consequences of industry consolidation including changes in R&D productivity are not examined. As a further research topic, measuring these changes to the R&D productivity will be quantified.

Among companies with least R&D productivity, some companies have not selected industry consolidation and sustained the business. By analyzing these companies, sustainability of business model and R&D productivity can be considered.

Two-stage DEA methods are employed in this thesis, the value will be varied with parameters including the number of companies, R&D spending, product value, the length of measurement period. Changes of each company in the RDP map on annual basis can be measured using the malmquist index method. In this way, changes in R&D productivity for each company

can be quantified and can be used as a R&D risk management tool.

5.5. Limitations

Regarding limitations of this dissertation, notably there are many other factors besides R&D productivity with respect to the industry consolidation process. Since only large, publicly listed pharmaceutical companies were followed, a potential bias toward company size should be recognized. This paper uses NPVs forecasted by Barclays Capital and the shape of the RDP map will be different if forecasts from other entities are used. Due to the issue of data availability, NMEs undergoing clinical trials are excluded even though such NMEs are an important component of R&D productivity. Thus, this dissertation shows only the R&D productivity of companies positioning themselves within the industry. Some academic researches explain that complementing the therapeutic categories is a crucial factors and there are other strategic rationales for the industry consolidation process. Any significant investments to improve the lifecycle of existing products may distort the RDP map, though such cases were not observed. Regarding DEA analysis, it is limited because it does not measure absolute efficiency; the analysis is sensitive to data selection and parameters. Finally, Ward et al.[39] mention that measuring R&D productivity requires some considerations such as sample data, timeframe, and type of analysis.

5.6. Conclusion

Based on these results and limitations, employing the RDP map enables us to measure an individual company's R&D productivity with two dimensions, and visualize relative status in the pharmaceutical industry. The issue for the pharmaceutical industry today is to improve R&D productivity, especially cost efficiency. To overcome this issue, selection of appropriate therapeutic categories and strategic alliances, including M&A and academic collaboration, will become more important. While there are several useful R&D management tools, the RDP map provides another way to inspect current R&D strategy; it shows how to improve productivity by complementing either cost efficiency or product value effectiveness, or both.

At least two lessons can be learned from this dissertation. First, to sustain R&D productivity over the long term, companies should focus on dominant therapeutic franchises while balancing cost efficiency and product value effectiveness. As shown by the antibiotics development case during the 1980s, lifestyle diseases during the 1990s in Japan, vaccines in 2007, and cancer and respiratory in 2012 within the global pharmaceutical industry, therapeutic category selection plays an important role in companies' R&D strategy and impacts R&D productivity. Second, if a company becomes less optimal or fails significantly to catch up with the benchmark, it is likely to pursue M&A or seek an alternative way to improve R&D productivity.

Verifying improvement of corporate value through M&A has been an important research topic. The methodology developed in this dissertation enables management to monitor changes in R&D productivity relative to the benchmark, understand causes of any dispersion, and consider appropriate measures to resolve issues.

Managements can monitor changes in R&D productivity relative to the industry benchmark as well as regularly analyze how each R&D program affects companies' overall R&D productivity. This dissertation also helps health care professionals and scientists monitor progress for each R&D program using the same parameters and understand the reasons for any dispersion from the benchmark. The outcomes may help managements allocate resources efficiently.

5.7. Acknowledgement

I would like to express my special gratitude to my advisor Professor Dr. Hiromichi Kimura and Dr. Sachiko Masuda. I appreciate for encouraging my research and for allowing me to grow as a research scientist. I would also like to express my gratitude to my committee members, Dr. Hiroyuki Arai, Dr. Hiroyuki Kusuhara, Dr. Kiichiro Tsutani, Dr. Shunsuke Ono, and Dr. Masuhiro Kato for serving as my committee members even at hardship and for their comments and suggestions. I would also like to express my gratitude to Dr. Kazuhisa Sekimizu for his suggestions.

Bibliography

1. Lindgardt Z., Reeves M., Wallenstein J. Waking the giant: business model innovation in the drug industry. *InVivo*, 2008. pp. 1-6.
2. Pammolli F., Magazzini L., Riccaboni M. The productivity crisis in pharmaceutical R&D. *Nature Review Drug Discovery*, 2011. pp. 428-38.
3. Garnier P., Rebuilding the R&D engine in big pharma. 2008. pp. 68–79.
4. DiMasi J., Hansen W. & Grabowski G., The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 2003. pp. 151-185.
5. Sann-Dodd F., Is poor research the cause of the declining productivity of the pharmaceutical industry? An industry in need of a paradigm shift. *Drug Discovery Today*, 2013. pp. 211-7.
6. DiMasi J., Faden L. Factors associated with multiple FDA review cycles and approval phase times. *Drug Information Journal*, 2009. pp. 201-225.
7. Scannell J.W., Blanckley A., Boldon H. et al. Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Review Drug Discovery*, 2012. pp. 191-200.
8. DiMasi J., Success rates for new drugs entering clinical testing in the United States. *Clinical Pharmacology and Therapeutics*, 1995. pp. 1-14.
9. DiMasi J., Risks in new drug development: approval success rates for investigational drugs. *Clinical Pharmacology and Therapeutics*, 2001. pp. 297-307.
10. Struck M., Biopharmaceutical R&D success rates and development times. *Biotechnology*, 1994. pp. 674-7.
11. *The Pharmaceutical Industry in Figures, 2010 Edition*. Brussels : European Federation of Pharmaceutical Industries and Associations, 2010, pp. 5-8.
12. Kaitin I., Obstacles and Opportunities in New Drug Development. *Clinical Pharmacology and Therapeutics*, 2013. pp. 210-2.

13. Milligan P.A., Brown M.J. et al. Model-Based Drug Development: A rational Approach to Efficiently Accelerate Drug Development. *Clinical Pharmacology and Therapeutics*, 2013. pp. 502-514.
14. Patel C., Coyle J. Building a New Biomedical Ecosystem: Pfizer's Centers for Therapeutic Innovation. *Clinical Pharmacology and Therapeutics*. 2013. pp. 1-3.
15. Drew J., Innovation deficit revisited: reflection on the productivity of pharmaceutical R&D. *Drug Discovery Today*, 1998. pp. 491-4.
16. Bunnage, M.E. Getting pharmaceutical R&D back on target. *Nature Chemical Biology*, 2011. pp. 335-9.
17. LaMattina, J.L. The impact of mergers on pharmaceutical R&D. *Nature Review Drug Discovery*, 2011. pp. 559-60.
18. Geisler E., An integrated cost-performance model of research and development evaluation. *Omega*, 1995. pp. 281-294.
19. Brown G., Svenson A., Measuring R&D productivity. *Research Technology Management*, 1998. pp. 30-35.
20. Hashimoto A., Haneda S. Measuring the change in R&D efficiency of the Japanese pharmaceutical industry. *Research Policy*, 2008. pp. 1829-36.
21. Elebring T., Gill A., Plowright T. What is the most important approach in current drug discovery: doing the right things or doing things right? *Drug Discovery Today*, 2011. pp. 1166-9.
22. Empfield R., Leeson D. Lesson learned from candidate drug attrition. *IDrugs*, 2011. pp. 869-73.
23. Paul S.M., Mytelka D.S., Dunwiddie C.T., et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Review Drug Discovery*, 2011. pp. 428-438.
24. Morgan S., Grootendorst P., Lexchin J., Cunningham C. The cost of drug development: A systematic review. *Health Policy*, 2011. pp. 4-17.

25. DiMasi J., Grabowski H., Vernon J. R&D costs and Returns by Therapeutic Category. *Drug Information Journal*, 2004. pp. 211-23.
26. Adams C., Brantner V. Estimating The Cost Of New Drug Development: Is It Really \$802 Million? *Health Affairs*, 2006. pp. 420-8.
27. Higin M.J., Rodriguez D. The outsourcing of R&D through acquisition in the pharmaceutical industry. *Journal of Financial Economics*, 2006. pp. 351-383.
28. Danzon P.M., Epstein A., Nicholson S. Mergers and Acquisitions in the Pharmaceutical and Biotech Industries. *Managerial and Decision Economics*, 2007. pp. 307-328.
29. Andrade G., Mitchell M., Stafford E. New evidence and perspectives on mergers. *Journal of Economic Perspectives*, 2001. pp. 103-120.
30. Ravenscraft D.J., Long W.F. Paths to creating value in pharmaceutical mergers. [ed.] Kaplan S.N. Chicago: University of Chicago Press, 2000.
31. Demirbag M., Ng C-K., Ekrem T. Performance of Mergers and Acquisitions in the Pharmaceutical Industry: A Comparative Perspective. *Multinational Business Review*, 2007. pp. 41-61.
32. Ornachi G. Mergers and innovation in big pharma. 2009. pp. 70-9.
33. Mahlich J., The Japanese pharmaceutical industry in transition: Has higher research orientation resulted in higher market value? *Asian Business & Management*, 2007. pp. 75-94.
34. Sakakibara K., Tsujimoto M. Why did R&D productivity of the Japanese firms decline? (in Japanese). Economic and Social Research Institute, 2003. pp. 1-20.
35. L.G., Thomas. Are we all global now? Local vs foreign sources of corporate competence: The case of the Japanese pharmaceutical industry. *Strategic Management Journal*, 2004. pp. 865-886.
36. Mitchell W., Roehl T., Slattery R.J. Influences on R&D growth among Japanese pharmaceutical firms, 1975–1990. 1995. pp. 17-31.

37. Charnes A., Cooper W.W., Rhodes, E. Measuring the efficiency of decision making units. *European Journal of Operations Research*, 1978. pp. 429-444.
38. Ward D.J., Martino O.I., Simpson S., Stevens A.J. Decline in new drug launches: myth or reality? Retrospective observational study using 30 years of data from the UK. *BMJ Open*, 2013. pp. 1-6.
39. Chen Y., Zhu J. Measuring information technology's indirect impact on firm performance. *Information Technology Management*, 2004. pp. 9-22.
40. Wang C.H., Gopal R.D., Zionts S. Use of data envelopment analysis in assessing information technology impact on firm performance. *Annals of Operations Research*, 1997. pp. 191-213.
41. Charnes A., Cooper W.W., Rhodes, E. Measuring the efficiency of decision making units. *European Journal of Operations Research*, 1978. pp. 429-444.
42. Andersen P., Petersen N. A procedure for distance efficient units in data envelopment analysis. *Management Science*, 1993. pp. 30-35.
43. Banker D., Charnes A., Cooper W. Some models for estimating technical and scale inefficiencies in data envelopment analysis. *Management Science*, 1984. pp. 1078-92.
44. S., Malmquist. Index numbers and indifference surfaces. 1953. pp. 209-42.
45. Caves D.W., Christensen L.R., Diewart W.E. The econometric theory of index numbers and the measurement of input, and output productivity. *Journal of Economic Theory*, 1982. pp. 1393-1414.
46. Fare R., Lovell C. Measuring the technical efficiency. *Journal of Economic Theory*, 1978. pp. 150-62.
47. Kao C., Hwang S-N. Efficiency decomposition in two-stage data envelopment analysis: An application to non-life insurance companies in Taiwan. *European Journal of Operations Research*, 2008. pp. 418-429.
48. Odagiri H, Murakami N. Private and quasi-social rates of return on pharmaceutical R&D in Japan. *Research Policy*, 1992. pp. 335-45.

49. Haneda S., Odagiri H. Appropriation of returns from technological assets and the values of patents and R&D in Japanese high tech firms. 1998. pp. 303-321.
50. European Federation of Pharmaceutical Industries and Associations. The Pharmaceutical Industry in Figure. 2010.
51. Ishibashi T., Kusama M., Sugiyama Y., Ono S. Analysis of regulatory review times of new drugs in Japan: association with characteristics of new drug applications, regulatory agency, and pharmaceutical companies. *Journal of Clinical Pharmacy and Therapeutics*, 2012. pp. 657-773.
52. Ringel M., Tollman P., Hersch G., Schulze U. Does size matter in R&D productivity? If not, what does? *Nature Reviews Drug Discovery*, 2013. pp. 901-902.
53. Shimura H., Masuda S., Kimura H. A lesson from Japan: research and development efficiency is a key element of pharmaceutical industry consolidation process. *Drug Discovery and Therapeutics*, 2014. pp. 57-63.
54. Shimura H., Masuda S., Kimura H. R&D productivity map: visualization of the current industry landscape. *Journal of Clinical Pharmacy and Therapeutics*, 2014.
55. DiMasi J., Grabowski H. Economics of new oncology drug development. *Journal of Clinical Oncology*, 2007. pp. 209-16.
56. Saranga H., Banker R.D. Productivity and technical changes in the Indian pharmaceutical industry. *Journal of Operations Research Society*, 2010. pp. 1777-88.

APPENDIX

Appendix 1 List of new molecular entities approved in Japan from 1980 to 2006

Year	Company	New Molecular Entities
1980	Pfizer/Taito	Tinidazole
1980	Sumitomo/Kowa	Prazepam
1980	Lederle	Trazodone Hydrochloride
1980	Sumitomo/Roche	Clonazepam
1980	Sumitomo	Fludiazepam
1980	Roche/Schering	Diflucortolone Valerate
1980	Takeda/Lederle	Trepibutone
1980	Dainippon	Canrenoate potassium
1980	Kodama	Insulin
1980	Kodama	Actrapid insulin
1980	Sankyo	Haloxazolam
1980	Meiji Seika	Fosfomycin Calcium Hydrate
1980	Daiichi	Adosterol
1980	Daiichi	Techne Pyrophosphate
1980	Green Cross	Polyethylene Glycol Treated Human Normal Immunoglobulin
1980	Nippon Zeki	Cideferron
1980	Kyorin	L-Carbocisteine
1980	Takeda/Bristol Banyu	Clidanac
1980	Chugai	Alfacalcidol
1980	Yamanouchi	Dantrolene sodium
1980	Kanebo	Prasterone sulfate sodium
1980	Otsuka	Carteolol hydrochloride
1980	Schering	Metrizamide
1980	Teijin	Ipratropium bromide
1980	Otsuka	Procaterol Hydrochloride Hydrate
1980	Dainippon	Enflurane
1980	Hoechst	Lyophilized Human Blood Coagulation Factor XIII Concentrate
1980	Green Cross/Abbott	Hepatitis B immune globulin
1980	Takeda/Ciba-geigy	Cefsulodin
1980	Takeda/Ciba-geigy	Cefotiam
1980	Nihon Kayaku	Peplomycin
1980	Meiji Seika	Fosfomycin sodium
1980	Daiichi	Techne Albumin
1981	Tokyo Tanabe/Hokuriku	Tulobuterol hydrochloride
1981	Nippon Shinyaku	Clofedanol Hydrochloride
1981	Taito Pfizer	Prazosin
1981	Otsuka	Econazole Nitrate
1981	Sumitomo/Up John	Pronalgon
1981	Daiichi	Cinepazide maleate
1981	Sumitomo	Clinofibrate
1981	Yamanouchi/Mitsui Seiyaku	Nicardipine hydrochloride
1981	Daiichi	Lofepamine hydrochloride
1981	ICI/Sumitomo	Tamoxifen Citrate
1981	Yoshitomi/Taito Pfizer	Bacampicillin Hydrochloride
1981	Yamanouchi/Yoshitomi/Essex	Sisomycin
1981	Shionogi	Vancomycin Hydrochloride
1981	Ajinomoto/Morishita	L-Histidine
1981	Nihon Merck Banyu	Dorzolamide Hydrochloride
1981	Fujisawa	Pilocarpine
1981	Dainippon	Loperamide hydrochloride
1981	Boehringer	Pirenzepine Hydrochloride Hydrate
1981	Nihon Kayaku/Alps	Aspalon
1981	Toyo Jozo	Eletomin
1981	Takeda	Oxendolone
1981	Teijin	Feprazone
1981	Daiichi	Ticlopidine hydrochloride
1981	Ciba-geigy	Maprotiline
1981	Toyama Chemical	Aclatonium napadisilate
1981	Rhodia	Acebutolol
1981	Green Cross	Exocoypol
1981	Yoshitomi	Pranoprofen
1981	Taiho	Hydrocortisone Sodium Succinate
1981	Yamanouchi/Mitsui Seiyaku	Carmofur
1981	Sanraku Ocean	Aclarubicin
1981	Nihon Medi-Physics	Krypton(81mKr) Generator
1981	Sankyo/Squibb	Halcinonide
1981	Fujisawa/SmithKline Fujisawa	Cimetidine
1981	Schering	Gestonorone
1981	Schering	Cyproterone acetate
1981	Sankyo	Buacamol hydrochloride
1981	Shionogi	Dobutamine Hydrochloride
1981	Sankyo/Sandoz	Metolazone
1981	Eisai	Tripamide
1981	Glaxo	Cefaloxime
1981	Toyama Chemical/Taito Pfizer	Cefoperazone sodium
1981	Hoechst/Roussel	Cefotaxime
1981	KyowaHakko/Santen	micronomicin sulfate
1981	Ciba-geigy	Cefroxadine
1981	Merck Banyu	Sulindac
1981	Fujisawa	Rhodopin
1981	Taito Pfizer	pirbuterol
1981	Tokyo Tanabe/Hokuriku	sulfadiazine
1981	Wyeth	Fentiazac
1981	Lederle	Amcinonide
1981	Schering	Biliscopin

Year	Company	New Molecular Entities
1981	Yoshitomi	Cargutoecin
1981	Shionogi	Lamoxef Sodium
1981	Fujisawa	Ceftizoxime Sodium
1981	Yoshitomi	Mezlocillin
1981	Shionogi	Cefaclor
1981	Kaken	Ferric Citrate Hydrate
1982	Kissei	Tranilast
1982	KyowaHakko	Domperidone
1982	Shionogi/Yamanouchi	Fenoprofen
1982	Toyama Chemical/Taito Pfizer	Piroxicam
1982	Green Cross	Aspirin di-lysine
1982	Eisai/Yamanouchi/Tokyo Tanabe	Chenodeoxycholic Acid
1982	Kowa	Prednisolone valerate acetate
1982	Schering	Isoconazole nitrate
1982	Banyu/Bristol Banyu	Cefadroxil
1982	Nihon Medi-Physics	Technetium(99mTc) Stannous Colloid
1982	Otsuka	Plas-Amino
1982	Lion	Butacetamide semisuccinate
1982	Toyo Jozo	Mequitazine
1982	Eisai	Eperisone hydrochloride
1982	Glaxo	Labetalol
1982	Tanabe	Afloqualone
1982	Tanabe	Fominoben hydrochloride
1982	Daiichi	Budralazine
1982	Fujisawa/Ciba-geigy	Metoprolol Tartrate
1982	Sankyo	Captopril
1982	Sankyo	Ketotifen fumarate
1982	Shionogi/Shinogi-Lilly	Cinoxacin
1982	Tokyo Tanabe/Hokuriku	Flufenamic acid
1982	Tokyo Tanabe/Hokuriku	Flufenamic acid
1982	Taisho	Hydrocortisone butyrate propionate
1982	Takeda	Cefmenoxime hydrochloride
1982	Sankyo	Mianserin hydrochloride
1982	Boehringer	Bunitrolol hydrochloride
1982	Roussel	Disopyramide Phosphate
1982	Sumitomo/Up John	Triazolam
1982	Kaken	Befunolol hydrochloride
1982	Tokyo Tanabe/Winthrop	Dainazol
1982	Asahi Kasei	Enocitabine
1982	Sumitomo/Up John	Clindamycin Hydrochloride
1982	Nihon Medi-Physics	Technetium(99m TC) Hydroxymethylenediphosphonate
1982	Kaken	Technetium
1983	Teijin	Ambroxol
1983	Otsuka	Buprenorphine hydrochloride
1983	Tobishi	Tolfenamic acid
1983	Ohara/Morishita	Emorfazone
1983	Fujisawa	Tolciclate
1983	Mitsui Seiyaku	Aloask
1983	Hisamitsu/Torii	Ibuprofen piconol
1983	Glaxo	Clobetasone Butyrate
1983	Yamanouchi	Cefotetan
1983	Yamanouchi	Cefotetan sodium
1983	Nihon Medi-Physics	Indium(111 In) Chloride
1983	Nippon Shinyaku	Estramustine Phosphate Sodium Hydrate
1983	Taiho	Tegsufur
1983	Nihon Zeki	Anti-Inhibitor Coagulant Complex
1983	Bristol Banyu/Nihon Kayaku	Cisplatin
1983	Dainippon/Kyorin	Urokinase(tissue culture)
1983	Roussel	Mitotane
1983	Sumitomo	Melinamide
1983	ICI/Sumitomo	Atenolol
1983	Yoshitomi	Etizolam
1983	Hoechst	Piretamide
1983	Otsuka	Flunisolide
1983	Maruho	Mueopolysaccharide polysulfuric acid ester
1983	Daiichi	Timiperone
1983	Eisai/Roche	Flunitrazepam
1983	Sankyo	Mexazolam
1983	Chugai/Mitsubishi Yuka	Nicorandil
1983	Takeda	Vinipocetine
1983	Kowa	Acemetacin
1983	Taisho	Sofalcone
1983	Kaken	Dinoprostone
1983	Taito Pfizer	Tioconazole
1983	Shionogi	Cefamandole
1983	Roussel	Tiaprofen
1983	Takeda/Up John/Sumitomo	Alplazolam
1983	Merck Banyu	Diflunisal
1983	Mitsui Seiyaku	Flutazolam
1983	Toyo Jozo	Mizoribine
1983	Mochida/Ajinomoto	Vidarabine
1983	Torii/Kyorin	Norfloxacacin
1983	Dainippon	Gliclazide
1983	Tanabe	Trimebutine Maleate
1984	Ono	Gemeprost
1984	Daiichi	Bucladesine Sodium
1984	Bristol Banyu	Colestimide
1984	Boehringer	Fenoterol
1984	Glaxo	Ranitidine
1984	Nihon Medi-Physics	Technetium(99m Tc) N'-pyridoxyl-5'-methyltryptophan
1984	Cutter	Globulin, human immune serum
1984	Daiichi/Otsuka/Dow Chemical	Probucol
1984	Sankyo/Sandoz	Guanfacine
1984	Sankyo	Naloxone
1984	KyowaHakko	Flunarizine hydrochloride
1984	Inabata/Kyoto	Indapamide

Year	Company	New Molecular Entities
1984	Hokuriku	Tiquizium bromide
1984	Eisai	Teprenone
1984	Green Cross	Globulin, antilymphocyte
1984	Hoechst	R-bulin
1984	Green Cross	HB Vaccine
1984	Daiichi	Malotilate
1984	Roche	Etretinate
1985	Ono	Camostat mesilate
1984	Kanebo	Cianidanol
1984	Yamanouchi	Famotidine
1984	Boehringer	Mexiletine Hydrochloride
1984	Hoechst	penbutolol sulfate
1984	Beecham	Amoxycillin
1985	Sumitomo/Wellcome	Aciclovir
1985	Mochida	Ulinastatin
1985	Shionogi	Ifosfamide
1985	Shionogi	Vindesine sulfate
1985	Toray	Ferron
1985	Banyu/Meiji Seika	Cleboipride Malate
1985	Yamanouchi	Diflorasone diacetate
1985	Daiichi	Ofloxacin
1985	Kaken	Dosulepin
1985	Sankyo/Essex	Netromycin
1985	Sumitomo/Yamaouchi	Cefpiramide sodium
1985	Toyama Chemical/Kaken	Cefbuperazone sodium
1985	Meiji Seika	Midecamycin acetate
1985	KyowaHakko	Astromicin sulfate
1985	Eisai	Bunazosin hydrochloride
1985	Sankyo/Sandoz	Freeze-dried pH4 treated human immunoglobulin
1985	Dainippon	Enoxacin
1985	Yoshitomi	Bromperidol
1985	Yamanouchi	Formoterol
1985	Wyeth/Taiho	oxaproxin
1985	Nihon Shoji	Guanabenz Acetate
1985	Meiji Seika	Amfencac sodium hydrate
1985	Dainippon/Squibb	Nadolol
1985	Travenol	Autoplex
1985	Sumito/Travenol	Freeze-dried ion-exchange-resin treated human normal immunoglobulin
1985	Bristol Myers	Butorphanol tartrate
1985	Mochida	Tofisopam
1985	Sadoz	Bromovincamine fumarate
1985	Sumitomo	Arctinolol
1985	Fujirebio	Moxisylyte
1985	Novo Nordisk	Insulin Actrapid
1985	Shionogi	Insulin Human
1985	Shionogi	Tilactase
1985	Roche	Calcitriol
1985	Schering	Iopamidol
1985	Mochida	Miconazole
1985	Mochida	Trilostane
1985	Shionogi	Clocapramine dihydrochloride
1985	Tokyo Tanabe/Kaken	Oxiconazole Nitrate
1985	Tanabe	Sulconazole Nitrate
1985	KyowaHakko	Dacarbazine
1985	Yamanouchi	lentinan
1985	Sandoz	Ciclosporin
1985	Green Cross	Haptoglobin
1985	Green Cross	Tetanobulin
1985	Sumitomo	Somatrem
1985	Sankyo	Loxoprofen sodium
1985	Roussel	Floctafenine
1985	Chugai	Löbenzarit Disodium
1985	Toyo Jozo/Torii	Sutoprofen
1985	Yamanouchi	Clenbuterol hydrochloride
1985	Kyorin	Troxipide
1985	Sankyo	Plaunotol
1985	Bayer	Bifonazole
1985	Roche	Ceftriaxone sodium
1986	Torii/Kyorin	Nafamstat mesilate
1986	Kissei	Ritodrine Hydrochloride
1986	Mitsubishi Kasei	Difluprednate
1986	Hokuriku/Maruho	Dexamethasone valerate
1986	Eisai	Azelastine hydrochloride
1986	Green Cross	Hyaluronic acid
1986	Fujisawa/SmithKline Fujisawa	Auranofin
1986	Kaken	Mabuterol hydrochloride
1986	Sumitomo/Kanabo	Flutoprazepam
1986	Banyu	Enalapril maleate
1986	Kaken/Taito	Sizofran
1986	Nihon Medi-Physics	N-Isopropyl-4-Iodoamphetamine(123I) Hydrochloride
1986	Galxo	Ceftazidime
1986	Taito Pfizer	Cefoperazone
1986	Teikoku Zoki	Roxatidine acetate hydrochloride
1986	Eisai	Sodium ferrous citrate
1986	Takeda	Idebenone
1986	Lederle	Felbinac
1986	Mochida/Ajinomoto	Cefpimizole sodium
1986	Torii/Kanebo	Lenampicillin hydrochloride
1986	Taito Pfizer	Sultamicillin tosylate
1986	Toyo Jyozo	Rokitamycin
1986	The Research Foundation for Microbial Diseases of Osaka University	Measles/Mumps/Rubella combined vaccine live attenuated
1986	Eiken Kagaku	Ioxaglic acid
1986	Taiho	Dexamethasone Propionate
1986	Mitsui Seiyaku	Aprindine
1986	Nihon Pharmaceutical	Eptazocine hydrobromide
1986	Banyu	Thibenzole
1986	KyowaHakko	ketoconazole

Year	Company	New Molecular Entities
1986	Ajinomoto	Elental
1986	Tokyo Tanabe	Ranimustine
1986	Squibb	Aztreonam
1986	Sumitomo	Interferon- α
1986	Squibb	Fludrocortisone
1986	Toyo Jyozo	Tiapride hydrochloride
1986	Boehringer	Azosemide
1986	Fujisawa	Tiapride Hydrochloride
1986	KyowaHakko	Oxatomide
1986	Bristol Myers/Nihon Kayaku	Etoposide
1986	Nihon Kayaku	Ubenimex
1986	Tanabe	Aspoxicillin
1986	Green Cross	Antithrombin III
1987	Daichi/Sterling Winthrop	Iohexol
1987	Schering	Iotrolan
1987	Up Johon	Ornoprostil
1987	Green Cross	Thiamine · Cobalt · Chlorophyllin Complex
1987	Takeda	Spizofurone
1987	Dainippon/Kyowa Hakko	Haloperidol decanoate
1987	Takeda	Amoxanox
1987	Roche	Tenoxicam
1987	Sante	Bucillamine
1987	Roche	Fansidar
1987	Roche	Doxifluridine
1987	Meiji Seika	Cefminox sodium
1987	Takeda/Lederle	Cefazonam
1987	Banyu/Torii	Imipenem Hydrate
1987	Toyama Chemical	Cefteram pivoxil granules
1987	Fujisawa	Cefixime
1987	Wellcome	Zidovudine
1987	Shionogi	Benexate hydrochloride betadex
1987	Schering	Lisuride
1987	Eisai/Mitsubishi Kasei	Bifemelan hydrochloride
1987	Mitsubishi Kasei	Repirinast
1987	Tokyo Tanabe	beractant
1987	Lederle	Mitoxantrone hydrochloride
1987	Esex	Interferon- α 2B
1987	Takeda/Roch	Interferon- α 2A
1987	Takeda	Carumonam sodium
1987	Ono/Kissei	Sodium ozagrel
1987	Yamanouchi/Essex	Indeloxazine hydrochloride
1987	Tanabe	Denopamine
1987	Dainippon/Ono	Limaprost
1987	Sandoz	Tizandine hydrochloride
1987	Otsuka	Clofazole
1987	Green Cross	Dexamethasone palmitate
1987	Taiho	Halopredone Acetate
1987	Fujirebio	Alminoprofen
1987	Toyo Jyozo/Essex	Isepamicin Sulfate
1987	Galxo	Cefaloxime
1987	Nihon Zeki/Hoechst	Fibrin glue
1987	Kodama	Oxybutynin chloride
1987	Shionogi	Alcemetasone dipropionate
1987	Oreganon	Vecuronium bromide
1987	Kissei	Terodiline hydrochloride
1987	Tanabe	Nicergoline
1987	Yamanouchi	Amosulalol hydrochloride
1987	Dainippon	Alacepril
1987	Roche	Midazolam
1987	SS	Flutropium bromide
1987	Janssen Kyowa	Mebendazole
1987	Bayer	Ciprofloxacin
1987	Tanabe	Amizet B
1987	Shionogi	Flomoxef sodium
1987	Meiji Seika/Sanraku	pirarubicin
1987	Banyu	Pneumococcal vaccine
1987	Kaketsuken	Recombinant Adsorbed Hepatitis B Vaccine
1987	Banyu/Shionogi	Recombinant Adsorbed Hepatitis B Vaccine
1988	Hoechst	Buserelin acetate
1988	Schering	gadopentetate dimeglumine
1988	Hoechst	Propentofylline
1988	Yoshitomi	fasudil hydrochloride hydrate
1988	Boehringer	Brotizolam
1988	Mochida	inosine pranobex
1988	Mochida/Otuka	Interferon
1988	Sumitomo	Somatropin
1988	Nippon Shinyaku	Irsogladine Maleate
1988	Takeda	Ipriflavone
1988	Kowa	Nipradilol
1988	Kaken	Urapidil
1988	Meiji Seika	Ethyl lofazepate
1988	Taiho	Miridacin
1988	Santen	Pivallephrine
1988	Bayer	Praziquantel
1988	Green Cross	Freeze-dried Human Anti-HBs Immunoglobulin
1988	Kyorin	Ibudilast
1988	Mitsui Seiyaku	Sultopride
1988	Takeda	Delapril hydrochloride
1988	Sumitomo	Somatorelin
1988	Fujisawa	Nivadipine
1988	Sumitomo	Droxidopa
1988	Rhone Poulanc	Benabax
1988	Danippon	Zonisamide
1988	Rhone Poulanc	Zopiban
1988	Taisho	Midodrine hydrochloride

Year	Company	New Molecular Entities
1988	Shionogi	Rilmazafone hydrochloride
1988	Sandoz	Octreotide acetate
1988	Sankyo	Pravastatin
1988	Yoshitomi/Janssen Kyowa	Cisapride
1988	Eisai	Nadide
1988	Tobishi	Batroxobin
1988	Nihon Medi-Physics	Technetium(99mTc) Human Serum Albumin Diethylenetriamine Pentaacetic Acid
1988	Amersham	Technetium Tc-99m Exametazime
1988	Farmitalia Carlo Erba	Epirubicin hydrochloride
1988	Mitsubishi Kasei	Terazosin hydrochloride
1988	Yamanouchi	Propafenone Hydrochloride
1988	Pfizer	cis-Furconazole
1989	Dainippon/Ciba-Geigy	Cardralazine
1989	Lederle	Felbinac
1989	Mochida	Setiptiline
1989	Fujisawa	Budesonide
1989	Shionogi/Schering-Plough	Dilevalol
1989	Sankyo	Cefpodoxime proxetil
1989	Shionogi	Interferon Gamma-1a
1989	Sankyo/Kirin	Epoetin Alfa
1989	Chugai	Epoetin beta (genetical recombination) preparation
1989	Pfizer	Doxazosin Mesilate
1989	Bayer	Nisoldipine
1989	Yoshitomi	Nitrendipine
1989	Daiichi/Mitsubishi Kasei	Argatroban
1989	Dainabot	Isoflurane
1989	Maruishi	Sevoflurane
1989	Merrell Dow	Terfenadine
1989	Shionogi/Horukiku	Lomefloxacin hydrochloride
1989	Toyama/Dainabot	Tosufloxacin tosilate
1989	Yamanouchi/Teikoku Zoki	Calcitonin Salmon
1989	Earth	Levocarnitine chloride
1989	Mochida/Nihon Suisan	Ethyl ionsapentate
1989	Fujisawa/SmithKlineBeecham	Nabumetone
1989	Takeda	Cefotiam hydrochloride
1989	Sintec	Ganciclovir
1989	Taiho/Hoechst	Cefodizime Sodium
1989	Bristol Myers	Carboplatin
1990	E. Lilly/Zeria	Nizatidine
1990	Takeda	Manidipine Hydrochloride
1990	Otsuka	Vesnarinone
1990	Schering/Wyeth	Lormetazepam
1990	Hoechst	C1 inactivator
1990		Varicella virus antigen
1990	Sumitomo	Disodium ethidronate
1990	Otsuka	Rebamipide
1990	Roche	Cilazapril Hydrate
1990	Tanabe	Bisoprolol hemifumarate
1990	Fujisawa	Cifenline succinate
1990	Boehringer	Oxitropium bromide
1990	Tori/Wakamoto	Tazanolast
1990	Meiji Seika	Arbekacin
1990	Yoshitomi/Fujisawa/Fujisawa Astra	Omeprazole Sodium
1990	Asahi Kasei/Kowa	Tissue-type plasminogen activator
1990	Kissei/Boehringer	Bezafibrate
1990	Yoshitomi	Mosapramine Hydrochloride
1990	Tokyo Tanabe/Bristol Myers Squibb	Pemirolast
1990	Roussel	Roxithromycin
1990	Nihon Medi-Physics	Iodine
1990	Mitsubishi Kasei	Recombinant Adsorbed Hepatitis B Vaccine
1990	KyowaHakko/Mitsubishi Kasei	Alteplase
1990	Toyobo	silteplase
1990	Suntory	Pilsicainide Hydrochloride Hydrate
1990	Yamanouchi	Nemonapride
1990	Eisai	Indometacin farnesil
1990	Abbott	Clarithromycin
1990	Janssen Kyowa	Muromonab-CD3
1991	Fuji Chemical	Monethanolamine Oleate
1991	Sakai Chemical	Polydocanol
1991	Dainippon	Ameziumin metilsulfate
1991	Shionogi/ICI	Lisinopril
1991	Eisai/3M	Flecainide
1991	Kanebo	Trazodone hydrochloride
1991	Zeria	Mycobacterium tuberculosis extract
1991	Daiichi	Romurtide
1991	ICI	Goserelin acetate
1991	Green Cross/Morinaga Milk	Mirimostim
1991	Bayer	Globulin, human immune serum
1991	Yoshitomi	nasaruplase
1991	Banyu	Simvastatin
1991	KyowaHakko	Benidipine hydrochloride
1991	KyowaHakko	Oxiglutatime
1991	Fujisawa	Cefdimir
1991	Sankyo/Kirin	Granulocyte-colony stimulating factor
1991	Chugai	Lenograstim
1991	Kaketsuken	Freeze-dried Concentrated Human Blood Coagulation Factor IX
1991	Teika/Kowa	Sucrose · Povidone-Iodine
1991	Teysan	Xenon(¹³³ Xe) Gas
1991	Ono	Epalrestat
1991	Yamanouchi/Kaken/Toray	Beraprost sodium
1991	Kissei	Heparin (LMW) (Dalteparin)
1991	Yamanouchi	Flumazepil

Year	Company	New Molecular Entities
1991	Kaken/Hisamitsu	Butenafine hydrochloride
1991	SmithKline Beecham	Granisetron Hydrochloride
1991	Mallinkrodt	Ioversol
1991	Suntory	Sapropterin Hydrochloride
1991	SS/Teikoku	Deprodone
1991	Toyama Chemical/Nissin Seiyaku	Tilisolol hydrochloride
1991	Kaken/Green Cross	Flurbiprofen axetil
1991	Kissei/Ono	Ozagrel hydrochloride
1991	Takeda	Celmoleukin
1991	Shionogi	Tecleleukin
1991	Suntory	Interferon-γ1A
1992	Bristol Myers Squibb	Didanosine
1992	Nihon Medi-Physics	Technetium(99mTc) Galactosyl Human Serum Albumin Diethylenetriamine Pentaacetic Acid
1992	Amersham	Indium oxycincholin
1992	Taisho	Amiodarone Hydrochloride
1992	Takeda	Leuprolide acetate
1992	Nippon Shinyaku	Celiprolol hydrochloride
1992	Wakado	Diazepam
1992	Yamanouchi	Mepirodipine hydrochloride
1992	Oreganon	bepiridil hydrochloride
1992	Sandoz	Mazindol
1992	Bristol Myers Squibb	Hydroxycarbamide
1992	Yamanouchi/Meiji Seika/Sterling Winthrop	Dopamine Hydrochloride
1992	Mitsubishi Kasei/Sante Labo	Betaxolol Hydrochloride
1992	Nihon Kayaku	Cytarabine
1992	Unitika	Thrombin Factor VII
1992	Shionogi/Schering-Plough	Ceftibuten capsules
1992	Lederle/Nissin Seifun	Tocoretinate
1992	Daiichi	3'-Iodobenzylguanidine
1992	Takeda	Laprazol
1992	Roche	Cefetamet pivoxil hydrochloride
1992	Tanabe/Sintec	Enprostil
1992	Nihon Medi-Physics	15-(4-Iodophenyl)-3-(R,S)-Methylpentadecanoic Acid (123I)
1992	Daiichi/Boehringer	Carvedilol
1992	Ciba-Geigy	Benazepril
1992	Bristol Myers Squibb	Fluphenazine
1993	Sarle	misoprostol
1993	Otsuka	Nadifloxacin
1993	Roche/Toyama Chemical	Aniracetam
1993	Taiho	Propiverine Hydrochloride
1993	Daiichi	echmetium (99mTc) Hexakis (2-Methoxy-Isobutyl Isonitrile)
1993	Nippon Shinyaku/Nihon Pharmaceutical	Iodine
1993	Daiichi	meta.iodobenzylguanidine
1993	Ciba-Geigy/Kanebo	Emedastine Fumarate
1993	Fujisawa	Tacrolimus
1993	Sandoz	Bopindolol
1993	Janssen Kyowa	Itraconazole
1993	Mitsubishi Kasei	Sarpogrelate Hydrochloride
1993	Sadoz	terbinafine hydrochloride
1993	SS	Neticonazole
1993	Bayer	Octocog alfa
1993	Nihon Chemiphar/Zeria	Zaltoprofen
1993	Dainippon	Sparfloxacin
1993	Nihon Shoji	sorivudine
1993	Sumitomo	Duteplase
1993	Yamanouchi	Tamsulosin hydrochloride
1993	Shionogi	Cefpirome Sulfate
1993	Kyorin	Fleroxacin
1993	Shionogi	Albunex
1993	Bayer	Acarbose
1993	Toyama Chemical/Pfizer	Ampiroxicam
1993	Shionogi/Schering-Plough	Mometasone furoate
1993	Tanabe/Schering	Imidapril hydrochloride
1993	Tanabe	Ecabet Sodium Hydrate
1993	Yamanouchi	Zinostatin stimalamer
1993	Sankyo/Alps	Panipenem
1993	Kyorin	Amorolfine Hydrochloride
1993	Pfizer/Sumitomo	Amlodipine besylate
1993	Teijin	Tacsalcitol
1993	Mitsubishi Kasei/Torii	Betamethasone butyrate propionate
1993	Daiichi	Levofloxacin hydrate
1993	SmithKline Beecham	Albendazole
1993	Shionogi	Efonidipine hydrochloride ethanolate
1993	Sankyo/Glaxo	Ondansetron
1993	Yakult/Daiichi	Irinotecan Hydrochloride Hydrate
1993	Yoshitomi/Japan Tobacco	Azasetron hydrochloride
1993	Hokuriku	Tulobuterol
1993	Nihon Kayaku	guspertimus hydrochloride
1993	Daiichi	Technetium (99mTc) Macroaggregated Human Serum Albumin
1993	Toa Eiyo	Angiotensin II
1993	Daiichi	Technetium tc99m bicisate
1993	Bristol Myers Squibb	Meglumine Gadopentetate
1993	Amersham	Tetrofosmin
1994	Mitsubishi Kasei/Nippon Shinyaku	Actarit
1994	Ciba-Geigy	Disodium pamidronate
1994	Eisai	lomepril
1994	Yamanouchi	Isosorbide Mononitrate
1994	Sankyo	Temocapril Hydrochloride
1994	Boehringer	Epinastine Hydrochloride
1994	Zenyaku	Sobuzoxane
1994	KyowaHakko	Nartograstim (Genetical Recombination)

Year	Company	New Molecular Entities
1994	Kaketsuken	Pentostatin
1994	Meiji Seika	Cefditoren Pivoxil
1994	Takeda	HB Vaccine
1994	Tsumura	Triethylenetetramine
1994	Nippon Shinyaku/Wyeth	Etodolac
1994	Boehringer	Pimobendan
1994	Sanwa Kagaku	Propagermanium
1994	Glaxo	Fluticasone Propionate
1994	Takeda	Voglibose
1994	Zeria	polaprezinc
1994	E. Lilly	Pergolide
1994	Taiho/Toso Akzo	Mofezolac
1994	Tsumura	Latoconazole
1994	Ueno	Isopropyl unoprostone
1994	Fujisawa	Mecasermin
1994	Mitsubishi Chemical	Corticotropin
1994	Banyu	Indometacin sodium
1994	Tanabe	Docarpamine
1994	Shimizu	Heparin (LMW) (Parnaparin)
1994	Warner Lambert	Pirfenol
1994	Lederle	Photofrin
1994	Shionogi	Uromitexan
1994	Nihon Kayaku	Flutamid
1994	Schering	Terguride
1994	Denka/化学及	Aimnugen
1994	Roche	Tretinoin
1994	Mochida	Astemizole
1994	Taiho	Suplatast Tosilate
1994	Syntec	Nafarelin acetate
1994	Hoechst/Ciba-Geigy	Felodipine
1994	Suntory	Atrial natriuretic peptide
1994	Nihon Kayaku	Toremifene
1994	Nihon Chemiphar	Bevantolol
1994	Ono	Pranlukast hydrate
1994	Pharmacia	Idarubicin Hydrochloride
1995	Bristol Myers Squibb	Cefepime hydrochloride
1995	Shionogi	Nedaplatin
1995	Sumitomo	Meropenem
1995	Asahi Kasei	Fasudil
1995	Takeda	Cefozopran Hydrochloride
1995	Hokuriku	Itopride Hydrochloride
1995	Ciba-Geigy	Fadrozole
1995	Yoshitomi	Quinapril
1995	Rhone Poulanc	Lymphoglobuline
1995	Ajinomoto/Boehringer	Cilnidipine
1995	Zeneca	Propofol
1995	Takeda	Serabenasat
1995	Chugai	Ioxilan
1995	Sankyo	Troglitazone
1995	Nihon zoki	Globulin, antilymphocyte
1995	Daiichi	Myosin dethylenetriaminopentaacetic acid Indium
1995	Eisai	Olprinone hydrochloride
1995	Roussel/Hoechst	Trandolapril
1995	SmithKline Beecham	Mupirocin
1995	Taiho	Aramidipine
1995	Tanabe	Iopromide
1996	Novo Nordisk	Glucagon
1996	Baxter	Factor VIII concentrates
1996	Kyorin/Nishin Seifun	Mesalazine
1996	Boehringer	Talipexole
1996	Daiichi	Gadodiamide Hydrate
1996	Janssen Kyowa	Risperidone
1996	Meiji Milk	Hepatitis B vaccine
1996	Dainippon	Ebastine
1996	Mochida/Mitsui Seiyaku	Nateplase
1996	Roche	Zalcitabine
1996	Genzyme	Alglucosase
1996	Yamanouchi	Milrinone
1996	Sumitomo	Tandospirone citrate
1996	Yamanouchi	Ramosetron hydrochloride
1996	Allergan	Botulinum toxin
1996	Otsuka	IFN-gamma
1996	Rhone Poulanc	Docetaxel
1996	Ciba-Geigy	Clofazimine
1996	Wellcome	Lamivudine
1996	Banyu	Indinavir sulfate ethanolate
1996	Astra	Foscarnet
1997	Banyu/Teijin	Alendronate
1997	Yamanouchi/Suntory	Faropenem sodium
1997	Shionogi	Cefcapene pivoxil hydrochloride hydrate
1997	Yamanouchi	Incafonate
1997	Sanofi/Sankyo/Yamanouchi	Pentazocine
1997	Eiken Chemical	Ferumoxides
1997	Bristol Myers Squibb	Paclitaxel
1997	Bristol Myers Squibb	samivudine
1997	Roche	Saquinavir Mesilate
1997	Novartis	Tropisetron
1997	Eisai	Sodium rabeprazole
1997	Dainabot	Ritonavir
1997	Servier/Daiichi	Perindopril Erbumine
1997	Maruishi	nitroprusside
1997	Torii/Japan Tobacco	Nelfinavir mesilate

Year	Company	New Molecular Entities
1997	Genzyme	imiglucerase
1998	Taiho	Indometacin Farnesil
1998	Hoechst Marion Roussel	teicoplanin
1998	Eisai	Monteplase
1998	Dainippon	Mosapride Citrate Hydrate
1998	Daiichi/UCB	Ceterizine hydrochloride
1998	Fujisawa	Cefoselis
1998	Novartis	Fluvastatin
1998	Fujimoto	Selegiline
1998	Banyu	Losartan
1998	Nippon Shinyaku	Portolac
1998	Bristol Myers Squibb	Sotalol
1998	Nihon Kayaku	Colforsin dapropate hydrochloride
1998	Boehringer	Nevirapine
1998	Yamanouchi	Tissue-type plasminogen activator (Pamiteplase)
1998	Rhone Poulanc-Roerer	Riluzole
1998	Alcon	Apraclonidine hydrochloride
1998	Asahi Kasei/Roche	Naftopidil
1998	Wellcome	Epoprostenol sodium
1998	Pfizer	Sildenafil
1998	Taiho	Tegafur, Gimeracil, Oteracil Potassium
1998	Takeda/Bayer	Cervastatin
1998	Kotobuki	egualen sodium hydrate
1998	KyowaHakko	Vinorelbine ditartrate
1998	Banyu	Dorzolamide hydrochloride
1998	Roche/Yoshitomi	Torasemide
1998	Pharmacia	Lomerizine
1998	Glelan	Fenofibrate
1998	Pharmacia	Latanoprost
1998	Zeneca	Bicalutamide
1998	E. Lilly	Gemcitabine Hydrochloride
1998	Takeda	Candesartan cilexetil
1998	Mitsubishi Chemical	Colestimide
1999	Meiji Seika/Solvay Meiji	Fluvoxamine maleate
1999	Yamanouchi/Schering	Levonorgestrel / Ethinylestradiol
1999	Lederle/Teikoku Zoki	Levonorgestrel ethinylestradiol
1999	Oreganon	Desogestrel / Ethinylestradiol
1999	Mitsui Seiyaku	Nifekalant
1999	Yamanouchi	Nateglinide
1999	Janssen Kyowa	Levocabastine hydrochloride
1999	Otuka	Carbon-13-urea
1999	Lederle	Levofolinic acid
1999	Tanabe/Schering	mixture of Galactose - Palmitic acid
1999	SS	Quazepam
1999	Kissei	Cabergoline
1999	Kissei	Amprenavir
1999	Banyu	Efavirenz
1999	Glaxo Wellcome	Abacavir
1999	Asahi Kasei	Milnacipran Hydrochloride
1999	UCB/Taiho	piracetam
1999	Roche	Mycophenolate Mofetil
1999	Takeda	Pioglitazone Hydrochloride
1999	Hoechst Marion Roussel	Glimepiride
1999	Mitsui Seiyaku	Heparin (LMW) (Reviparin)
1999	Schering/Knorr	Fludarasbine
1999	Eisai	Donepezil hydrochloride
1999	Glaxo Wellcome	Zanamivir Hydrate
1999	Glaxo Wellcome	Sumatriptan
1999	Taiho/Fujirebio	Lafutidine
1999	Taitoku Zoki	Calcipotriol Hydrate
1999	Solvay/Zenyaku	Liranaftate
1999	Warner Lambert	Delavirdine
1999	Novo Nordisk	Factor VIIa concentrates
1999	Takeda/Senju	Bromfenac sodium hydrate
1999	Yamanouchi/Warner Lambert	Atorvastatin calcium
1999	Pfizer	Azithromycin Hydrate
1999	Bayer	Ramatroban
1999	Dainippon	Clobazam
2000	Tanabe	Taltirelin
2000	Daiichi	Iodixanol
2000	Kyorin	Levobunolol hydrochloride
2000	Hokuriku/Fujisawa	Polycarbophil Calcium
2000	Oreganon	Heparinoid (LMW) (Danaparoid)
2000	Tanabe	Betotastine besylate
2000	Chugai	Maxacalcitol
2000	Glaxo Wellcome	Valaciclovir
2000	Schering	Interferon-β1B
2000	Kaketsuken	Protein C, activated
2000	Sanofi Sante Labo/Fujisawa	Zolpidem
2000	Wakamoto	Acitazanolast Hydrate
2000	Eiken Chemical	Meglumine
2000	SmithKline Beecham	Paroxetine Hydrochloride Hydrate
2000	Ciba-Geigy	Valsartan
2000	Hoechst Marion Roussel	Fexofenadine
2000	Bayer	Ciprofloxacin
2000	Dainabot	Lopinavir
2000	AstraZeneca	Quetiapine fumarate
2000	Roche	Oseltamivir Phosphate
2000	KyowaHakko	Olopatadine Hydrochloride
2000	Boehringer	Meloxicam
2000	Sumitomo	Perospirone hydrochloride
2000	Taiho	Lornoxicam
2000	AstraZeneca	zafirlucast
2000	E. Lilly	Olanzapine
2000	SmithKline Beecham	Topotecan

Year	Company	New Molecular Entities
2000	AstraZeneca	Anastrozole
2001	SS	Mefloquine
2001	Roche	Trastuzumab Emtrastine (Genetical Recombination)
2001	Pharmacia	Linezolid
2001	AstraZeneca	Omeprazole
2001	Kaken	Trafermin (recombinant) Preparation
2001	Sumitomo/Taiisho	Falcalecicriol
2001	Mitsubishi Tokyo Seiyaku	Edaravone
2001	AstraZeneca	Ropivacaine
2001	Toyama Chemical/Taiho/Otsuka	Tazobactam sodium/piperacillin sodium
2001	Chugai/Zenyaku	Rituximab
2001	E. Lilly	Insulin Lispro
2001	Daiichi/Nihon Kayaku/Snow Brank Milk	Cevimeline Hydrochloride Hydrate
2001	Kyorin/Banyu	Montelukast Sodium
2001	AstraZeneca	Zolmitriptan
2001	Janssen Kyowa/Kyowa Hakko	Fentanyl
2001	Saraya	Equilibrium mixture containing 6% Peracetic acid
2001	Novo Nordisk	Insulin aspart
2001	Mitsubishi Welpharma/SS	fudosteine
2001	Yamanouchi/Amgen	Interferon alfacon-1
2001	Meiji Seika/Wyeth Lederle	Biapenem
2001	Johnson & Johnson	o-Phthalaldehyde
2001	Schering Plough	Ribavirin
2001	Ciba-Geigy	Imatinib Mesilate
2001	Aventis	Dalofopristin
2001	Tanabe	Infliximab
2001	Tanabe	Imidapril Hydrochloride
2001	Ciba-Geigy	Basiliximab
2001	Janssen	Cladribine
2001	Takeda/Ajinomoto	Sodium risedronate hydrate
2001	Dainabot	Palivizumab
2001	Pfizer	Eletriptan hydrobromide
2002	Kyorin	Gatifloxacin Hydrate
2002	Sumitomo	Amrubicin hydrochloride
2002	Toyama Chemical/Mitsubishi Welpharma	Pazufloxacin mesilate
2002	Glaxo SmithKleine	Salmeterol Xinafoate
2002	Ono	Sivelestat sodium hydrate
2002	Ono	Landioliol Hydrochloride
2002	Schering Plough	Loratidine
2002	Nagase Chemtecs	Landioliol
2002	Pharmacia	exemestane
2002	Schering Plough	Loratidine bulk
2002	AstraZeneca	Gefitinib
2002	Schering	ferucarbotran
2002	Maruishi	esmolol hydrochloride
2002	Meiji Seika/Nippon Shinyaku	Prulifloxacin
2002	Nihon Kayau	Freeze-dried BCG vaccine
2002	Alcon	Brinzolamide
2002	Banyu	Ivermectin
2002	Fujisawa	Micafungin sodium
2002	Boehringer	Telmisartan
2002	Sankyo	Azelinidipine
2002	Chugai/Kirin	Sevelamer Hydrochloride
2003	Glaxo SmithKleine	Sumatriptan
2003	Aventis	Lefunomide
2003	Chugai	Capecitabine
2003	Kowa	Pitavastatin Calcium
2003	Kyorin	Benzoic acid rizatriptan
2003	Aventis	telithromycin
2003	Boehringer	Pramipexole
2003	Aventis	Insulin Glargine
2003	Ciba-Geigy	Verteporfin
2003	Chugai	Peginterferon Alfa-2a
2003	Meiji Seika	Laserphyrin
2003	Pfizer	Fosfluconazole
2003	Abbott/Maruishi	Dexmedetomidine hydrochloride
2003	E. Lilly	Raloxifene
2003	Nissin Kyorin	Indiseron Hydrochloride
2003	Sankyo	Olmesartan Medoxomil
2003	Genzyme	Agalsidase
2003	Kissei/Takeda	Mitiglinide
2003	Torii/Japan Tobacco	Tenofvir disoproxil fumarate
2004	Bayer	Vardenafil hydrochloride hydrate
2004	Nihon Mediphysics	Iomazenil
2004	Novartis	Zoledronic acid hydrate
2004	Kaken	Pralmorelin hydrochloride
2004	Pfizer	Tiotropium bromide hydrate
2004	Glaxo SmithKleine	Adefovir Dipivoxil
2004	MSD	PegIntron
2004	Tanabe Mitsubishi	Valganciclovir hydrochloride
2004	Glaxo SmithKleine	Fosamprenavir Calcium Hydrate
2004	Takeda/Wyeth	Etanercept
2004	Shionogi	Rosuvastatin
2004	Yakult	Oxaliplatin
2004	Torii/Japan Tobacco	Emtricitabine
2004	Torii/Japan Tobacco	Tenofvir Disoproxil Fumarate
2005	Pola Pharma	Luliconazole
2005	Tobishi	Tamibarotene
2005	Chugai	Toclizumab
2005	Daiichi	Adenosine
2005	MSD	Follitropin beta
2005	Actellion	Bosentan hydrate
2005	Pfizer	Voriconazole
2005	Shionogi	Doripenem Hydrate

Year	Company	New Molecular Entities
2005	Nihon Mediphsics	Fludeoxyglucose (18F)
2005	Tanabe Mitsubishi	Freeze-dried live attenuated measles-rubella combined vaccine
2005	Pfizer	gemtuzumab
2005	Fuji Yakuhin	Inulin
2005	MSD	Finasteride
2005	Sanwa Kagaku	Miglitol
2005	Bayer	Moxifloxacin hydrochloride
2005	Otsuka	Aripiprazol
2005	Sanofi	Sulfuric acid clopidogrel
2005	Takeda/Kissei	Sildenafil
2005	Merck Sereno	follitropin alfa
2005	Novartis	Letrozole
2006	Pfizer	sertraline hydrochloride
2006	Yamanouchi	Succinic acid solifenacin
2006	Nihon Kayaku	Cetorelix acetate
2006	Yamanouchi	Tolterodine tartrate
2006	Biogen	Interferon beta-1a
2006	Bristol Myers Squibb	Entecavir
2006	Pfizer	Gabapentin
2006	MSD	Temozolomide
2006	Otuka	Mozavaptan hydrochloride
2006	Dainippon Sumitomo	Agalsidase alfa
2006	DaiichiSankyo	Perfluorobutane
2006	Takeda/Janssen	Bortezomib
2006	Genzyme	Laronidase
2006	Baxter	Ruriotocog alfa
2006	Janssen	Remifentanyl hydrochloride
2006	GSK	Ropinirole hydrochloride
2006	MSD	Pneumococcal vaccine

Appendix 2 List of new molecular entities used for global pharmaceutical companies in 2007

Franchise	Clinical Stage		
	Marketed	Filed	Phase III
Analgesic	Jurista	CS1401E	MK-0974
Analgesic	Prialt	Trexima	PN400
Analgesic			Vicodin SR
Anti-Infective		Doripenem	
Anti-Infective		Geninax	
Anti-Infective		Teravancin	
Anti-Infective		Zeven	
Anti-Infective	Atripia		ABF656
Anti-Infective	Eraxis		Aurograb
Anti-Infective	Naxafil		CDA
Anti-Infective	Selzentry		Clevudine
Anti-Infective	Tyzeka		DL8234
Anti-Infective			E-5564
Anti-Infective			Gracevit
Anti-Infective			Mycograb
Anti-Infective			TAK-242
Anti-Infective			TFP561
Anti-Infective			TLT
Anti-Infective			TOBI TPI
Anti-Infective			Vicriviroc
Anti-Infective			YM643
Anti-Infective			Zithomax/chloroquin
Cancer	Ariance	Avastin	Acrelizumab
Cancer	Arranon	Tarceva	AG-13
Cancer	Ixabepilone		AMG531
Cancer	Sprycel		Asentar
Cancer	Sutent		AZD4054
Cancer	Tasigna		CP675206
Cancer	Tykerb		Denosumab
Cancer	Vectibix		E-7389
Cancer			Enzastaurin
Cancer			EP0906
Cancer			Gleevec
Cancer			HMR1275
Cancer			Humaxcd20
Cancer			Javlor
Cancer			Lumiliximab
Cancer			Mage A3
Cancer			MDX-010
Cancer			MK-8669
Cancer			Omitarg
Cancer			Pazopanib
Cancer			Promacta
Cancer			RAD001
Cancer			Recentin
Cancer			Rituximab RA
Cancer			S-1
Cancer			Sarasar
Cancer			Simuvax
Cancer			SOM230
Cancer			STA-4783
Cancer			Trovax
Cancer			VEGF Trap program
Cancer			Xaliproden
Cancer			XRP6258
Cancer			XRP9881
Cancer			Zactima

Franchise	Clinical Stage		
	Marketed	Filed	Phase III
Cardiovascular	Arixtra	Avapro	ABT335
Cardiovascular	Ex-forge	Azor	ABT335+Crestor
Cardiovascular	Letairis	Cordaptive	Acadesine
Cardiovascular	Tekturna	MK0524b	Apixaban
Cardiovascular		Regadenoson	AZD6140
Cardiovascular		Satavaptan	Clivarine
Cardiovascular		Simcor	Crestor+ABT333
Cardiovascular		Vernakalant	FTY720
Cardiovascular			KW3902
Cardiovascular			Lotrel
Cardiovascular			MK7418
Cardiovascular			Multaq
Cardiovascular			Noratak
Cardiovascular			Novoferon
Cardiovascular			Prasugrel
Cardiovascular			SCH530348
Cardiovascular			SSR 126517
Cardiovascular			Synordia
Cardiovascular			Tadalafil
Cardiovascular			TAK-475
Cardiovascular			TAK-491
Cardiovascular			Veletri
Cardiovascular			XRP0038
Central Nervous System	Avonex	Adapalene	Arocyte
Central Nervous System	Inovelon	Bifepurnox	Asenapine
Central Nervous System	Rozrem	Emend	ASP8825
Central Nervous System	Tysabri	Gapirone ER	BQ-12
Central Nervous System		Lamictal XR	Casopirant
Central Nervous System		Lunesta	Dianicine
Central Nervous System		MK-0517	E-2007
Central Nervous System		Org 25969	Emibegron
Central Nervous System		Pristiq	Eplivanserin
Central Nervous System		Rimonabant	FK-506
Central Nervous System		Seroquel XR	LY-2448686
Central Nervous System		Stilnoxium CR	Mylinax
Central Nervous System			Org 50081
Central Nervous System			Rituximab MS
Central Nervous System			Rosiglitazone XR
Central Nervous System			Saredutant
Central Nervous System			SUN Y7017
Central Nervous System			Teriflunomide
Central Nervous System			Valinanserin
Central Nervous System			Valoxan
Dermatology		Acomplia	Tracleer
Dermatology		Avandia	Acomplia+met
Diabetes	Galvus	Cimzia	AERx
Diabetes	Janumet	Entereg	AIR
Diabetes	Januvia	Galvus+met	AS-3201
Diabetes	Levemir	Pargluva	Atacand
Diabetes			Byetta
Diabetes			CS-011
Diabetes			CS-886dm
Diabetes			Dapagliflozin
Diabetes			Liragltuide
Diabetes			Saxagliption
Diabetes			SYR322
Gastrointestinal	Mircera	Methylnatrexone	BAY794980
Gastrointestinal			Gasmotin
Gastrointestinal			Mepolizumab
Gastrointestinal			Novoseven
Gastrointestinal			TAK390MR

Franchise	Clinical Stage		
	Marketed	Filed	Phase III
Hematology	Lybrel	Recalbon	Apprela
Hematology		Viviant	Arzoxifene
Hormone control		Prograf MR	Belatacept
Hormone control			ED-71
Hormone control			MK-0822
Hormone control			Org 36286
Hormone control			Pulminiq
Immune system		Careram	Actemra
Immune system		D2E7	ACZ885
Immune system		Raheara	Aranesp
Inflammation	Lucentis	Febuxostat	Belimumab
Inflammation			CNTO 148
Inflammation			Ocerelizumab
Inflammation			Prexige
Inflammation			SUN 0588r
Metablism		CP-945	
Metablism		KES-524	
Metablism		Taranabant	
Obesity	Macugen	AVS	Visudyne
Ophthalmic		DD-723	HGF
Respiratory		Toviaz	Asamanex+Foradil
Respiratory			Avodart
Respiratory			Claritin+Singulair
Respiratory			Creon
Respiratory			Flutiform
Respiratory			Immunotherapy
Respiratory			QAB149
Respiratory			sdmanex+foradil
Respiratory			Xatral
Urinary			Ceravix
Urinary		Flumist	
Urinary		Focetria	
Vaccine	Cervarix	Globoxix	ChimeriVax
Vaccine	Gardail	H5 N1 pandemic flu	Dengue vaccine
Vaccine	H5 1 pandemic flu		Hib-MenCY
Vaccine	Proquad		HIV AP
Vaccine	Rotarix		IC51
Vaccine	Rotateq		Men ACWT
Vaccine	Zostatvax		Menveo
Vaccine			Numax
Vaccine			Optaflu
Vaccine			Simplirix
Vaccine			Synthorix
Others	Veramyst	S-7701	YM484
Others		Xolair	

Appendix 3 List of new molecular entities used for global pharmaceutical companies in 2012

Franchise	Marketed	Clinical Stage	
		Filed	Phase III
Anti-infective	Rapiacta		RG7128
Anti-infective	Inavir		dolutegravir
Anti-infective			MK-3415A
Anti-infective			Moxidectin
Anti-infective			Zithromax/Chloroquine
Anti-infective			E5564
Anti-infective			S-349572
Cancer	Caprelsa	Bosutinib	AVE8062
Cancer	Halaven	Crizotinib	GSK1120212
Cancer		Axitinib	GSK2118436
Cancer		Yervoy (Ipilimumab)	PKC412 (AML)
Cancer		PLX4032	enzastaurin
Cancer		ASP3550	Necitumumab (IMC-11F8)
Cancer			Dacomitinib
Cancer			Ramucirumab (IMC-1121B)
Cancer			Elotuzumab
Cancer			T-DM1
Cancer			BSI-201 (PARP inhibitor)
Cancer			galiximab
Cancer			SOM230 (acromegaly)
Cancer			Oncovex
Cancer			Tykerb (adjuvant BC)
Cancer			Arzerra (RA)
Cancer			Brivanib
Cancer			Ridaforolimus
Cancer			Linifanib (ABT-869)
Cancer			Afinitor/RAD001
Cancer			Aflibercept (VEGF Trap)
Cancer			AMG-386
Cancer			pertuzumab
Cancer			AMG706
Cancer			MDV3100
Cancer			AMG386
Cancer			TAK-700
Cancer			Brentuximab Vedotin
Cancer			ARQ 197
Cancer			MORAb-003
Cardiovascular	Multaq	Ezetimibe/atorvastatin	Voraparxar
Cardiovascular	Tredaptive	HGF DNA plasmid	otamixiban
Cardiovascular	Brilinta	Eliquis (Apixaban)	Tredaptive/simvastatin
Cardiovascular	Edarbi	DU-176b	AVE5026 (ultra LWMH)
Cardiovascular		Kynapid (RSD1235)	Tyrisa
Cardiovascular			Anacetrapib
Cardiovascular			S-3013
Cardiovascular			Effient
Cardiovascular			TAK-085
Central Nervous System	Potiga	Remoxy	TC-5214
Central Nervous System	Memary	Proemend	mGlu2/3 (LY 2140023)
Central Nervous System	Cymbalta	Lunesta	NERI/Edivoxetine
Central Nervous System	Rivastach		Suvorexant
Central Nervous System	Reminyl		bapineuzumab
Central Nervous System	Rozerem		Preladenant
Central Nervous System			teriflunomide (MS)
Central Nervous System			BG-12
Central Nervous System			Solanezumab
Central Nervous System			Sovrima
Central Nervous System			E0302
Central Nervous System			FTY720 (MS)
Central Nervous System			Latuda
Central Nervous System			Lu AA21004
Central Nervous System			E2007

Franchise	Clinical Stage		
	Marketed	Filed	Phase III
Dermatology			ocrelizumab RA
Diabetes	Tradjenta	Janumet XR	Empagliflozin (BI 10773)
Diabetes	Ryzodeg		Dapagliflozin
Diabetes	Tresiba		albiglutide
Diabetes	Nesina		Dulaglutide
Diabetes			AVE0010 (GLP-1)
Diabetes			ASP1941
Diabetes			Janumet
Diabetes			AS-3201
Diabetes			Victoza - diabetes
Diabetes			SYR-322
Gastrointestinal		YM443	MLN0002
Gastrointestinal		Nexium	
Hematology	Factor XIII	Feraheme	Promacta
Hematology			Hematide
Hormone Control	NOMAC		Viviant
Hormone Control			Elonva
Hormone Control			Odanacatib
Hormone Control			SUN11031
Immune system			Zenapax (Daclizumab)
Inflammation	Nulojix	denosumab	Careram
Inflammation	Actemra		fostamatinib
Inflammation			ocrelizumab
Inflammation			Tofacitinib
Inflammation			Saforis
Metabolism	Prolia	Creon	
Metabolism		ASP1585 (AMG223)	
Obesity		Contrave	ATL-962
Respiratory	Dulera		QMF149
Respiratory	Symbicort		QVA149
Respiratory			Relovair
Respiratory			'719+'444
Urinary		Urief	
Urinary		YM178	
Vaccine		MenHibrix	Herpes Zoster Vaccine
Vaccine			HPV V503
Vaccine			V212
Vaccine			V419
Others	Bridion	ASP8825	MitraClip
Others		Tafluprost	Taliglucerase alfa
			Tafamidis