Original Article

DOI: 10.5582/ddt.8.57

A lesson from Japan: Research and development efficiency is a key element of pharmaceutical industry consolidation process

Hirohisa Shimura, Sachiko Masuda, Hiromichi Kimura*

Pharmaco-Business Innovation Laboratory, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan.

Summary **Scholarly attention to pharmaceutical companies' ability to sustain research and development (R&D) productivity has increased as they increasingly handle business challenges. Furthermore, the deterioration of R&D productivity has long been considered a major cause of mergers and acquisitions (M&As). This study attempts to investigate quantitatively the possible causes of the deterioration and the relationship between the deterioration and M&As by examining the Japanese pharmaceutical industry. Japan from 1980 to 1997 is an ideal case because of the availability of official data, but more importantly the significant changes in its business environment at the time. Using the Malmquist Index and data envelopment analysis, we measured the deterioration of R&D productivity from 1980 to 1997 based on a sample of 15 Japanese companies. Two lessons can be learned from Japan's case. First, to sustain R&D productivity over the long term, companies should use licensing activities and focus on the dominant therapeutic franchises. 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. These findings appear similar to the current situation of the global pharmaceutical industry, although Japan pursued more licensing activities than M&A to improve R&D productivity.**

Keywords: R&D productivity, industry consolidation, Japanese pharmaceutical industry, data envelopment analysis

1. Introduction

Scholarly attention to pharmaceutical companies' ability to sustain research and development (R&D) productivity has increased as they increasingly handle challenges such as escalating R&D expenditure, a lack of new molecule entities (NMEs), and cost containment schemes by payors (*1,2*). Indeed, R&D expenditure in the pharmaceutical industry has increased rapidly (*3,4*), but the number of NMEs entering the market has declined (*5-11*). Some argue that the rising cost was due to the complex nature of clinical trials while development risk remained fairly stable from the 1970s to 1990s (*12-14*).

Among Japan, Europe, and the United States, R&D spending declined most in Japan. Japanese companies spent 5,161 million yen in 1990 and 12,760 million yen in 2010. European companies spent 7,766 million euros in 1990 and 27,796 million euros in 2010. U.S. companies spent 6,803 million dollars in 1990 and 40,688 million dollars in 2010. Meanwhile, R&D productivity in terms of NME development declined most in Japan as well. Japanese, European, and U.S. pharmaceutical companies developed 74, 88, and 49 NMEs, respectively between 1990 and 1994, and 36, 89, and 77 NMEs between 1995 and 2000 (*15*). Consequently, in an attempt to address the deterioration of R&D productivity, Japanese pharmaceutical companies started pursuing mergers and acquisitions (M&As) since 1995 (Table 1).

However, although the deterioration of R&D productivity has long been considered a major cause of M&As (*16-18*), few studies have investigated quantitatively the possible causes of the deterioration and the relationship between the deterioration and M&As. This study attempts to address this gap in

**Address correspondence to:*
Dr. Hirohisa Shimura, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 103-0023, Japan.
E-mail: msubozeman@yahoo.co.jp

Table 1. List of antibiotics approved in Japan from 1980 to 1999

	Subclass code					Total
	611	612	613	614	624	
1980-1989						
Japan Origin	2	3	17	2	3	24
Import	0	1	10	0	1	11
Licensed-in	4	1	10	0	2	15
Total	6	5	37	2	6	50
1990-1999						
Japan Origin	1	1	7	1	3	10
Import	1	0	2	2	0	5
Licensed-in	0	0	2	0	0	2
Total	2	1	11	3	3	17
Total						
Japan Origin	3	4	24	3	6	34
Import	1	1	12	2	1	16
Licensed-in	4	1	12	0	2	17
Total	8	6	48	5	9	67

the literature by examining the case of the Japanese pharmaceutical industry.

In analyzing the relationship between the deterioration of R&D productivity and industry consolidation, the Japanese pharmaceutical industry is an ideal example for at least four reasons. First, the deterioration of R&D productivity in this industry accelerated after the 1990s. Second, except when Merck obtained a minority share in Banyu in 1982, the industry did not have M&As until 1997. Third, Japanese companies developed 30 globally available NMEs in the 1980s and 1990s. The main interest of their R&D programs shifted from antibiotics in the 1980s to drugs for lifestyle diseases such as high cholesterol, hypertension, and diabetes in the 1990s (Table 2). Finally, Japan provides many official data sources. It has a universal health care coverage system, and the Ministry of Health and Welfare (MHLW) approves and sets the price for each drug to be reimbursed by patients. The MHLW also provides ethical drug production statistics for 34 efficacy classes and 177 subclasses (Table 3). Finally, 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 4 is a list of the number of NMEs approved by the MHLW. Antibiotics represented more than 10% of the total NMEs approved in the 1980s. However, this share dropped sharply in the 1990s because of the pharmaceutical companies' focal shift to lifestyle diseases. In this study, we verify the relationship between lifestyle drug franchises and the deterioration of R&D productivity. We consider antibiotics, digestive system, and various cardiovascular and metabolism franchises as lifestyle disease drugs.

Several studies have discussed the changes in R&D efficiency of Japanese pharmaceutical companies. One study showed that the Japanese domestic environment for pharmaceuticals changed radically from 1975 to 1995, which degraded the innovative capability of the companies (*19*). Another study emphasized the importance of understanding the dynamics of R&D investment strategies between 1975 and 1990 (*20*). Finally, one study measured and observed the deterioration of R&D productivity of Japanese pharmaceutical companies from 1983 to 1992 using a quantitative method (*21*). This study aims to investigate the possible causes of the deterioration of R&D productivity in the Japanese pharmaceutical industry in the 1990s and its consequences, using data envelopment analysis (DEA) and the Malmquist Index (*22,23*). Based on the scores from the Malmquist Index calculation, one-way ANOVA and Tukey-Kramer testing were conducted to identify the possible causes of R&D productivity deterioration from 1980 to 1997. The relationship between the deterioration of R&D productivity and M&As was also discussed.

2. Materials and Methods

2.1. *Three approaches to measure R&D productivity*

There are at least three approaches to measure R&D productivity: ratio analysis, least squares regression, and DEA. DEA is a mathematical programming approach for measuring relative efficiency, utilizing multiple inputs and outputs, while ratio analysis handles single inputs and outputs. The fundamental difference between the statistical 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. 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.

2.2. *Variables used in this paper*

In our DEA, we select one input and three output variables to measure R&D productivity: the actual R&D expenditure as the sole input, and the accumulated number of weighted NMEs approved by the MHLW, sales, and operating profit as the three output variables. Some studies employed a multiple-variable model with the number of patent and publication submissions as input (*21*). However, the publication strategy may vary among companies, and there is little relationship between these variables and actual sales. Thus, these variables are not satisfactory indicators of input. We,

Table 2. Breakdown of antibiotics production by code number

Code number	Description	% In antibiotics production amount in each year			
		1976	1981	1991	1997
611	Antibiotic preparations acting mainly on gram-positive bacteria	2.2%	0.5%	3.0%	4.5%
612	Antibiotic preparations acting mainly on gram-positive bacteria	0.3%	3.0%	4.8%	2.8%
613	Antibiotic preparations acting mainly on gram-positive, gram-negative bacteria	68.4%	79.2%	70.3%	63.9%
614	Antibiotic preparations acting mainly on gram-positive bacteria and mycoplasma	10.5%	6.3%	3.6%	9.8%
615	Antibiotic preparations acting mainly on gram-positive, gram-negative bacteria, rickettsia and chlamydia	10.1%	3.5%	1.6%	1.7%
616	Antibiotic preparations acting mainly on acid-fast bacteria	4.5%	3.2%	0.6%	0.4%
617	Antibiotic preparations acting mainly on acid-fast bacteria	0.3%	0.3%	0.8%	0.7%
619	Other antibiotic preparations (including mixed antibiotic preparations)	1.8%	2.2%	0.1%	0.1%
624	Synthetic antibacterials (after 1991)	0.0%	0.0%	15.3%	16.2%
618	Antibiotic preparation acting mainly on a malignant tumor (before 1990)	2.0%	2.0%	0.0%	0.0%

Table 3. List of Japanese originated drugs sold over 20 countries

Period	Company	Generic name	Category
1980s	Toyama Chemical	Piperacillin	Antibiotics
	Toyama Chemical	Cefoperazone	Antibiotics
	Yamanouchi	Nicardipine	Hypertension drug
	Shionogi	Oxacephalosporin	Antibiotics
	Chugai	Nicorandil	Angina drug
	Yamanouchi	Ceftizoxime	Antibiotics
	Yamanouchi	Cefotetan	Antibiotics
	Danippon	Enoxacin	Antibiotics
	Fujisawa	Cefixime	Antibiotics
	Daiichi	Ofloxacin	Antibiotics
	Kyorin	Norfloxacin	Antibiotics
	Yamanouchi	Famotidine	Digestive drug
	Sankyo	Cefpodoxime	Antibiotics
	Sankyo	Pravastatin sodium	Cholesterol lowering drug
1990s	Taisho	Clarithromycin	Antibiotics
	Chugai	Lenograstim	Immunostimulator
	Shionogi	Ceftibuten	Antibiotics
	Takeda	Lansoprazole	Digestive drug
	Takeda	Leuprorelin acetate	Cancer drug
	Fujisawa	Tacrolimus	immunosuppressive drug
	Yamanouchi	Tamusulosin	Urinary drug
	Dainippon	Sparfloxacim	Antibiotics
	Tanabe	Imidapril Hydrochloride	Hypertension drug
	Daiichi	Levofloxacin	Antibiotics
	Yakult	Irinotecan	Cancer drug
	Sumitomo	Meropenem	Antibiotics
	Eisai	Rabeprazole	Digestive drug
	Takeda	Candesartan cilexetil	Hypertension drug
	Eisai	Donepezil	Alzheimer drug
	Takeda	Pioglitazone	Diabetics drug

Table 4. List of industry consolidation events in Japan

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

instead, use the actual number of NMEs approved by the MHLW. The R&D expenditure of a particular year was averaged over three years to consider accounting time delay of R&D expenditure. The time lag between the R&D expenditure and its outcome was assumed to be eight years (*24,25*). The "Annual Statistical Survey on Trends in Pharmaceutical Production" published by the MHLW was employed to determine the number of drugs. An interview form provided by the company that seeks approval from the MHLW was employed to identify the originator of the drugs 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 (*10*). There are two basic methods for a company to receive approval from the MHLW: *i*) registering as an original drug developer

and *ii*) registering as a co-development partner. Because there was little information on the clinical stage of the licensed NMEs, we set the weight for a licensed-in NME as 50% and a co-development NME as 20% of the R&D expenditure prior to the NME's approval.

2.3. *Definition of the Malmquist Index and its components*

The Malmquist Index was employed to identify the historical change in R&D productivity since a historical trend of DEA scores of R&D productivity does not reveal the causes of changes (*23*). The Malmquist Index score (MI score) was 1.00 if there was no change in R&D productivity, less than 1.00 if there was any improvement in R&D productivity, and greater than 1.00 if there was any deterioration in R&D productivity. The MI score can be decomposed into two mutually exclusive scores: the efficiency change (EC) and frontier shift (FS) scores. 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 1.00. The Bartlett test of homogeneity of variances, ANOVA, and Tukey-Kramer test were conducted to identify causes of the deterioration of R&D productivity.

2.4. *Data exclusion criteria*

We selected 24 companies originally but obtained a final sample of 15 companies after applying the following exclusion criteria: *i*) availability of financial data and *ii*) significant change in management control. We selected 1980 as the start of the study period because this was when the MHLW started the current approval system and 1997 as the end of the period because this marked the end of the M&A period in Japan; data on R&D expenditure, sales, and operating profit after 1997 may be distorted due to post-M&A processes such as restructuring and R&D reviews.

3. Results and Discussion

3.1. *Deterioration of the R&D productivity of the Japanese companies from 1980 to 1997*

Table 5 shows that the R&D productivity of the 15 Japanese companies declined from 1980 to 1997 and that R&D expenditures that were 2.10 times greater were required in 1997 to generate the same level of output in 1980 (MI score = 2.10). This finding is similar to those of Hashimoto and Haneda (*3*). This 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).

3.2. *A relationship between the R&D productivity and antibiotics R&D strategy in 1980s*

The results of the ANOVA tests show that the changes in R&D productivity differed among companies that developed antibiotics in the 1980s ($p < 0.05$) and among companies that developed different antibiotics subclasses, that is, '613 and '624' ($p < 0.05$). However, continuing antibiotics research did not explain the dispersion of R&D productivity among the 15 Japanese companies (Table 6). Table 7 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. Table 8 shows similar results but does not show that a shift from one

Table 5. List of financial data for 15 companies in 1980 and 1997

Name	1980			1997		
	Sales	R&D Expense	Operating Profit	Sales	R&D Expense	Operating Profit
Chugai	71,353	2,531	11,293	164,102	21,986	17,098
Daiichi	73,596	2,880	10,201	232,565	22,951	42,125
Dainippon	53,195	2,204	3,265	137,595	10,511	6,508
Eisai	103,365	4,012	18,575	258,655	30,473	45,711
Fujisawa	155,906	4,841	27,230	215,162	28,262	19,772
Kaken	19,394	990	1,667	63,519	5,676	2,846
Nippon Shinyaku	34,636	1,194	4,238	48,201	6,513	3,299
Sankyo	187,196	4,135	21,422	462,551	33,583	126,002
Shionogi	142,304	5,837	17,345	211,679	25,518	15,363
Takeda	430,883	11,858	37,199	640,094	54,770	104,250
Tanabe	114,544	4,217	16,116	181,976	19,777	16,156
Tokyo Tanabe	22,936	326	2,921	43,414	3,475	3,485
Toyama Chemical	31,865	775	5,299	42,776	5,581	3,912
Yamanouchi	76,601	3,169	12,090	317,780	28,607	67,175
Yoshitomi	44,106	1,998	5,617	109,170	10,099	12,001
Average	104,125	3,398	12,965	208,616	20,519	32,380
St. Dev.	103,751	2,836	10,162	165,811	13,992	38,551

Table 6. List of drug developers and names of major approved products

Name	Sales in JPY million	Antibiotics			Lifestyle disease drug	Digestive drug	Major drug approved between 1980 and 1997
		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	Epoetin β
Daiichi	> 50	I	Y	New quinolone	I	L	Levofloxacin
Dainippon	> 50	I	Y	New quinolone	I	L	Flomoxef sodium
Eisai	> 100	N	N	No development	I	I	Teprenone
Fujisawa	> 100	I	Y	Cepham	I	L	Tacrolimus hydarate
Kaken	< 50	L	Y	Cepham	N	N	Beraprost sodium
Nippon Shinyaku	< 50	N	N	No development	N	I	Irsogladine maleate
Sankyo	> 100	I	Y	Both cepham and new quinolone	I	I	Pravastatin sodium
Shionogi	> 100	I	Y	Both cepham and new quinolone	L	L	Latamoxef sodium
Takeda	> 100	I	Y	Cepham	I	I	Lansoprazole
Tanabe	> 100	I	Y	Cepham	N	L	Imidapril hydorchoride
Tokyo Tanabe	< 50	N	N	No development	N	N	Ranimustine
Toyama Chemical	< 50	I	Y	Both cepham and new quinolone	L	I	Cefetram pivoxil
Yamanouchi	> 50	I	Y	Cepham	I	I	Famotidine
Yoshitomi	< 50	L	N	Cepham	I	L	Etizolam

Table 7. MI score of the R&D productivity for 15 Japanese companies in 1997 and its components of MI score

Company	Malmquist Index	Efficiency Change	Frontier Shift
Chugai	3.19	1.24	2.56
Nippon Shinyaku	2.69	1.06	2.55
Tokyo Tanabe	2.57	1.09	2.36
Fujisawa	2.50	1.32	1.90
Eisai	2.42	1.17	2.07
Toyama Chemical	2.29	1.12	2.04
Takeda	2.15	1.04	2.06
Sankyo	2.05	1.00	2.05
Tanabe	2.04	0.98	2.08
Kaken	1.86	0.84	2.21
Dainippon	1.68	0.81	2.06
Daiichi	1.61	1.00	1.61
Yoshitomi	1.57	0.79	1.99
Yamanouchi	1.51	0.82	1.84
Shionogi	1.40	0.75	1.86
Average	2.10	1.00	2.08

Table 8. Summary of statistical results on R&D productivity

	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**

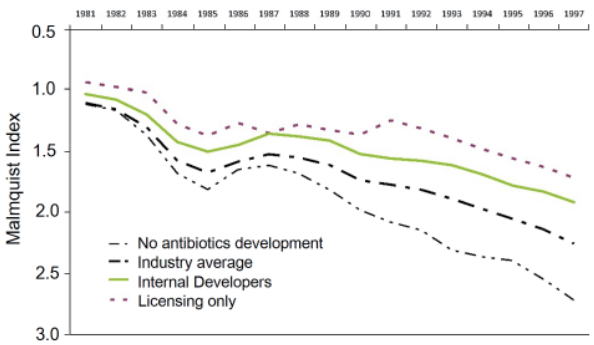

Figure 1. Trends of MI indices of R&D productivity grouped by antibiotics development strategies

subclass to another was a factor.

The results of our analysis suggest that the deterioration of R&D productivity was a major issue in the Japanese pharmaceutical industry and that involvement in antibiotics R&D helped sustain the R&D productivity of Japanese pharmaceutical companies in the 1980s. Figure 1 shows that the R&D productivity of companies utilizing licensing activities deteriorated, although the deterioration from 1980 to 1997 was not statistically significant.

3.3. *Interpretations of the R&D deterioration among Japanese companies using the Malmquist Index*

Table 9 shows the decomposition of the Malmquist Index into two components. It 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). These results suggest that licensing activities were more useful than internal development for Japanese companies in sustaining R&D productivity in the 1980s.

Furthermore, Table 10 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).

Pharmaceutical company 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 (Table 5). 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 will continue to pursue M&As in the near future. However, an M&A is not always an appropriate solution since the best fit may not be available at the time of decision making. Fujisawa, which had the fourth-worst MI score, withdrew its generic drug business from the United States in 1998. This study showed that the R&D productivity deterioration in the industry may explain why companies with the worst productivity scores entered into M&As within a few years of the deterioration. We conclude that 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.

3.4. *Implications for the current pharmaceutical industry*

Two lessons can be learned from Japan's case. First, to sustain R&D productivity over the long term, companies should use licensing activities and focus on the dominant therapeutic franchises, even on only the most advanced subclass. 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.

Though the study focused on the Japanese pharmaceutical industry from 1980 to 1997, it made a few interesting observations that can be applied to today's global pharmaceutical industry. The global industry seems to have entered a similar situation, but this assumption needs to be verified quantitatively. In the 1990s, research focus shifted from antibiotics to lifestyle disease drugs. Recently, this focus shifted to cancer and vaccine franchises. The number of NMEs approved by the U.S. Food and Drug Administration declined from 1996 to 2010. Thus, just as Japanese companies pursued licensing in the late 1980s to improve their R&D productivity, global companies sought M&As in the 2000s to sustain their R&D productivity. For example, Roche acquired leading cancer drug developer Genentech in 2008. To improve its R&D capability in anti-cancer drugs, Takeda acquired U.S. bioventure Millennium Pharmaceuticals in 2008 for 1 billion dollars. Likewise, to accelerate its vaccine research, Pfizer acquired Wyeth in 2009.

Due to the issue of data availability, we excluded NMEs undergoing clinical trials, even though such NMEs are an important component of R&D productivity. Thus, this study shows only the R&D productivity of companies positioning themselves within the industry.

Table 9. Statistical results of antibiotics development involvement in 1980s

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

Table 10. Average score of MI Index and its components, with subgroups defined by the company's antibiotics development strategy

	Malmquist Index	Efficiency Index	Frontier Shift Index
Average of companies with internally developed antibiotics	1.91	0.98	1.95
Average of companies licensed in antibiotics	1.71	0.82	2.10
Average of companies with only subclass 624 development	1.65	0.91	1.84
Average of companies with only subclass 613 development	1.95	0.97	2.02
Average of companies with both subclass 613 and 624 development	1.84	0.94	1.95
Average of companies with no antibiotics approval product	2.72	1.14	2.38

However, if internal data for ongoing R&D programs for each therapeutic franchise can be obtained, it is possible to monitor changes in R&D productivity within a company such as by using the net present value of each NME in the R&D expenditure by therapeutic class. In this way, management can not only monitor changes in R&D productivity relative to the industry benchmark but also analyze how each R&D program affects the company's overall R&D productivity regularly. This study also helps health care professionals and scientists monitor the progress of each R&D program using the same parameters and understand the reasons for any dispersion from the benchmark. The outcomes may help management allocate resources efficiently.

Sustaining R&D productivity has become a top priority of pharmaceutical companies. The methodology developed in this paper 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.

This study illustrated 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&As, 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 pharmaceuticals continues to decline. Our methodology will enable management to monitor changes in R&D productivity quantitatively and identify an appropriate R&D strategy.

3.5. *Limitations*

Despite using the DEA and Malmquist Index approaches, this study has at least two limitations. First, DEA does not measure absolute efficiency and is sensitive to data selection. Second, we selected the Japanese industry due to data availability. To obtain generalizable results on the relationship between the deterioration of R&D productivity and M&As, future studies should use a more recent global industry data set.

References

1. Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. Nature Rev Drug Discov. 2011; 10:428-438.
2. Bunnage E. Getting pharmaceutical R&D back on target. Nature Chem Biology. 2011; 7:335-339.
3. Lindgardt Z, Reeves M, Wallenstein J. Waking the giant: Business model innovation in the drug industry. In Vivo. 2008; 26:1-6.
4. Scannell W, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. Nature Rev Drug Discov. 2012; 11:191-200.
5. Garnier J. Rebuilding the R&D engine in big pharma. Harvard Bus Rev. 2008; 86:68-76.
6. DiMasi J, Faden L. Factors associated with multiple FDA review cycles and approval phase times. Drug Inform J. 2009; 43:201-225.
7. DiMasi J, Grabowski H. Economics of new oncology drug development. J Clin Oncol. 2007; 25:209-216.
8. DiMasi J, Grabowski H. The cost of biopharmaceutical R&D: Is biotech different? Manage. Decis Econ. 2007; 28:469-479.
9. Sam-Dodd F. Is poor research the cause of the declining productivity of the pharmaceutical industry? An industry in need of a paradigm shift. Drug Discov Today. 2013; 18:211-217.
10. DiMasi J, Hansen R, Grabowski H. The price of innovation: New estimates of drug development costs. J Health Econ. 2003; 22:151-185.
11. Dimitri N. An Assessment of R&D productivity in the pharmaceutical industry. Trends in Phamracol Sci. 2012; 12:683-685.
12. DiMasi J. Success rates for new drugs entering clinical testing in the United States. Clin Pharmacol Ther. 1995; 58:1-14.
13. DiMasi J. Risks in new drug development: Approval success rates for investigational drugs. Clin Pharmacol Ther. 2001; 69:297-307.
14. Struck M. Biopharmaceutical R&D success rates and development times. A new analysis provides benchmarks for the future. Biotechnol. 1994; 12:674-677.
15. European Federation of Pharmaceutical Industries and Associations. The Pharmaceutical Industry in Figures. 2010 ed., European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium, 2010; pp. 5-8.
16. Drew J. Innovation deficit revisited: Reflection on the productivity of Pharmaceutical R&D. Drug Discov Today. 1998; 11:491-494.
17. LaMattina L. The impact of mergers on pharmaceutical R&D. Nature Rev Drug Discov. 2011; 10:559-60.
18. Shimura H, Masuda S, Kimura H. Research and development productivity map: Visualization of industry status. J Clin Pharm Ther. 2014. Doi: 10.1111/jcpt.12126
19. Thomas G. Are we all global now? Local vs. foreign sources of corporate competence: The case of the Japanese pharmaceutical industry. Strat Mgmt J. 2004; 8-9:865-886.
20. Mitchell W, Roehl T, Slattery J. Influences on R&D growth among Japanese pharmaceutical firms, 1975-1990. J High Technol Manage Res. 1995; 1:17-31.
21. Hashimoto A, Haneda S. Measuring the change in R&D efficiency of the Japanese pharmaceutical industry. Res Policy. 2008; 37:1829-1836.
22. Charnes A, Cooper W, Rhodes E. Measuring the efficiency of decision making units. Eur J Oper Res. 1978; 2:429-444.
23. Zhu J. Quantitative Models for Performance Evaluation and Benchmarking: Data Envelopment Analysis with Spreadsheets. Springer Science+ Business Media, LLC, New York, USA, 2009; pp. 1-40.
24. Odagiri H, Murakami N. Private and quasi-social rates of return on pharmaceutical R&D in Japan. Res Policy. 1992; 21:335-345.
25. Haneda S, Odagiri H. Appropriation of returns from technological assets and the values of patents and R&D in Japanese high tech firms. Econ Innov New Techno. 1998; 7:303-321.

(Received January 8, 2014; Revised January 20, 2014; Re-revised January 21, 2014; Accepted January 24, 2014)