Acquisition of Drug Candidates in New Drug Development in Japan

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Abstract--**Open innovation (OI) is becoming a popular R&D management strategy in pharmaceuticals. In this study, we performed a comprehensive data collection on drug candidate acquisition, that has been the major OI mode during the drug development phase, in the Japanese pharmaceutical industry for the past 30 years. Our empirical analysis revealed that the acquisition of drug candidates has been widely conducted (accounting for a quarter of all newly developed compounds), and has contributed to more than half of launched products. Surprisingly, the acquisition of drug candidates has remained flat for the past 20 years; it has not increased in recent years despite the advocacy of OI. Acquisition at the preclinical stage was prevalent in the 1980s, and then late-stage acquisition started to increase and has dominated in recent years. There was no significant difference in therapeutic area distribution between in-house and outside-origin projects, suggesting that drug candidate acquisition was utilized mainly to reinforce internal R&D. Our findings can serve as a basis for discussion on the future direction of drug candidate acquisition in the Japanese pharmaceutical industry.**

I. INTRODUCTION

The open innovation (OI) strategy is described as the strategy that firms utilize and commercialize not only their own ideas but also inventions from external organizations [3]. This OI strategy has been increasingly used by the pharmaceutical industry [7][10][15][16][20][21]. This strategic shift from internal to open-source R&D in pharmaceuticals may be due to the following environmental difficulties. First, new drug development has high attrition rates [4], and the average developmental cost is continuously increasing [19][23]. Second, the patents of many high volume products expired around 2010 [8], requiring the reestablishment of profitable product pipelines. Third, the blockbuster model focusing on lifestyle-related diseases is in decline and is being replaced by a personalized and niche-market-oriented drug development model [1][25]. To overcome these challenging circumstances, pharmaceutical companies must improve their R&D productivity not only by relying on internal R&D but also by acquiring better technologies and more drug seeds/candidates from outside organizations.

There are many organizational modes for OI in pharmaceuticals at both the research and clinical development levels: research collaboration, outsourcing, consortia, in-licensing, co-development, M&A etc. [2][14]. Among those organization modes, acquisition of drug candidates (both by in-licensing and co-development) occupies a major place in the OI model of the pharmaceutical industry [21]. Approximately 25% of the project portfolios of big pharmaceutical companies are currently constituted by externally acquired drug candidates [21]. Licensed products and technologies share 20-25% of the sales in the top 12 US and EU pharmaceutical companies [18]. In the Japanese pharmaceutical industry, drug candidate acquisition has been reported to be the most important factor for openness in the industry [14]. Therefore, investigating drug candidate acquisition is quite important to understand the status and trend of pharmaceutical OI. In this study, we analyzed data for the past 30 years of drug candidate acquisition conducted in Japan, which is the second largest drug market in the world. This study contributes to managerial practice regarding how to improve R&D productivity in the pharmaceuticals by leveraging externally discovered drug candidates.

II. LITERATURE REVIEW

Much of the relevant literature addresses external collaborations and alliances in the pharmaceutical industry by using the term 'open innovation'. However, the scope of open innovation within the pharmaceutical industry varies in the OI literature. Current literature focuses on research collaboration through university-industry (U-I) relationships or consortia [15][16][24], drug candidate acquisition at the project level [21] and M&A [21], and a combination of various modes [2][7][14]. Because the focus in this study is drug candidate acquisition, we carefully selected and reviewed the OI literatures that analyzed drug candidate acquisition. In addition, there is some literature that describes drug candidate acquisition in the pharmaceutical industry without using the concept of OI. That literature is also reviewed in this section.

Bianchi et al. [2] reported that in- and out-licensing and development alliances were major modes of open innovation at the clinical development stages in the bio-pharmaceutical industry. The survey investigating the trend of open innovation in Japanese pharmaceutical companies revealed that Japanese pharmaceutical companies have actively conducted in-licensing of drug candidates to assemble the pipeline of target disease areas in the late 2000s [13]. This literature implies that drug candidate acquisition is one of the major paths for pharmaceutical companies to leverage external invention.

More detailed information on drug candidate acquisition (e.g., number of deals, time trend) was reported in several articles. Based on the recent analysis of 13 large multi-national pharmaceutical companies, Scuhmacher et al. [21] reported that 50% of their project portfolio was composed of externally acquired compounds, 25% by drug

candidate acquisition and 25% by company merger. This study suggested that the companies with a larger proportion of externally acquired projects generated higher earnings [21]. Gambardella et al. [6] investigated the balance of in-house and licensed projects in the pharmaceutical industries of the US and several EU countries in the 1990s. According to their report, the ratio of licensed projects to in-house projects was 20-60% with some variations among countries and years. The US market analyses in the mid-2000s stated that early-stage deals tended to increase although deals at phase 3 stage of clinical trials were still dominant [11][18]. For the Japanese pharmaceutical industry, Takatori et al. [22] reported that 40% of drug candidates under development in the top 10 Japanese pharmaceutical companies in 2009 were acquired from sources outside these organizations although no time trend was investigated and the detailed analysis was restricted to compound acquisition from small biotechnology companies. Hirai [9] reported the time trend of alliances from 1980 to 2000 in the Japanese pharmaceutical industry. In the study conducted by Hirai, alliances related to drug candidate acquisition were not distinguished from other alliances in the research and development stages (e.g., alliances related to technology and research tools).

As reviewed above, the existing literature consistently supported the observation that drug candidate acquisition has been continuously conducted in the world's pharmaceutical industries, and it accounted for a significant percentage of firms' project pipelines. However, the literature tracing the time trend is old, and recent papers do not cover the long-term trend. In addition, detailed characteristics, such as therapeutic areas of the deals and acquisition stages, have not been fully investigated. In this study, we performed a comprehensive data collection of drug candidate acquisition conducted by Japanese pharmaceutical companies over the past 30 years (1983 to 2012). We present our results from the analysis of the collected data and discuss the future direction of drug candidate acquisition within the Japanese pharmaceutical industry.

III. METHODOLOGY

The 'Asu no Shinyaku' (Tomorrow's New Drug) database (provided by TECHNOMICS, INC.) was the primary source for data collection. This database records clinically developed new drugs and drug candidates based on 30 years worth of information from press releases, news reports, scientific meetings and scholarly papers. We confirmed that this database covered 97% of new drugs approved in Japan after 2000 (data not shown). These data support the high trap efficiency of the database; however only approved drugs were searched. Database records provide both the name of the organization that originally created the drugs/drug candidates and the name of the company that conducted the clinical development of those drugs/drug candidates. Each record also provides the current developmental status, the stage of the drug project (the highest stage if failed or on-going), the disease application, the research and development details and the related papers. We first selected the drugs/drug candidates that were clinically developed by Japanese pharmaceutical companies (subsidiaries of foreign-affiliated companies were excluded). We omitted cases related to vaccine, generics and drug combinations. We then divided the drugs/drug candidates into two categories: (1) those acquired from outside organizations and (2) those originated in-house. We categorized the drugs/drug candidates by checking whether the organization creating the compounds was different from the company conducting the clinical development. Referencing the research and development details provided by the 'Asu no Shinyaku' database, we identified the year when the drug candidates were created in in-house-origin compounds and the year when the drug candidates were acquired in outside-origin compounds. In-house-origin compounds that were created from 1983 to 2012 and outside-origin compounds that were acquired from 1983 to 2012 were used for further analysis.

In each compound, we identified the current development status (launch, withdraw, on-going) and the highest development stage if withdrawn or on-going (pre-clinical, phase1, 2, 3). We also analyzed the time trend of in-house creation and acquisition based on the year when the compounds were created (in-house-origin) or acquired (outside-origin). To analyze the development stage of acquisition, we classified the compounds acquired from outside organizations by the clinical development stage at which the compounds were acquired. The disease application of each acquired compound was classified into 15 therapeutic areas as defined by 'Konnichi No Chiryoyaku (Current therapeutics)' (published by NANKODO). We also classified the disease application of internally-created compounds within the four Japanese pharmaceutical companies (Takeda, Eisai, Otsuka, Chugai) and compared the therapeutic area distribution between internally-created and acquired compounds by a chi-square test.

We used two other sources for data collection to confirm the recent acquisition trend observed from our 'Asu no Shinyaku' database analysis. We used the 'Cima-net' database (provided by CIMA SCIENCE JOURNAL, INC.), which records drugs/drug candidates developed by Japanese pharmaceutical companies, as the second source. We collected all new drugs/drug candidates with clinical development that was initiated between 2003 and 2012 from this database. We then classified the collected compounds into in-house-origin or outside-origin as indicated by the database. We compared the time trend of both categories based on the year when the clinical development was initiated because the accurate year of acquisition could not be identified in this database. Our third source was the 'Seiyaku Kigyo No Teikei Senryaku' (Alliance strategy of pharmaceutical companies) databook (published by Total Planning Center Osaka Corp.), which describes drug candidates acquired between 2007 and 2011 by the top 17 Japanese pharmaceutical companies. We counted the number

of drug candidate acquisitions conducted by the 17 companies in each year, and analyzed the time trend.

IV. RESULTS

A. Number and time trend of drug candidate acquisitions in the Japanese pharmaceutical industry

Table 1 shows the number of drug candidates that were created by in-house research and acquired from outside organizations between 1983 and 2012 in the Japanese pharmaceutical industry. The number was sorted according to the clinical development status (launch, failure or on-going) and the development stage if failed or on-going.

Drug candidate acquisition accounted for about one-fourth of clinically developed compounds. Interestingly, 46% of acquired drug candidates reached the market, which is much higher than the launch rate of internally-created drug candidates (9%); acquisition also yielded more launched drugs than in-house research (362 vs. 251 drugs).

Fig. 1 shows the time trend of the number of drug candidates that were created in-house or acquired from outside organizations from 1983 to 2012 by Japanese pharmaceutical companies.

The number of internally-created drug candidates has remained essentially unchanged over the past thirty years, with some fluctuations. In contrast, the number of acquired drug candidates increased in the early 1990s and then flattened out nearing 2012.

Because no increase of drug candidate acquisition was observed in recent years despite the advocacy of OI strategy, we confirmed the recent trend of drug candidate acquisition by using two different sources other than the 'Asu no Shinyaku' database. The analysis using the 'Cina-net' database revealed that the rate of acquired drug candidates in the total number of compounds developed by Japanese pharmaceutical companies from 2003 to 2012 has remained consistent throughout the time period (Fig. 2, left panel). The data obtained from the source published by Total Planning Center also revealed that the number of drug candidates acquired by the top 17 Japanese pharmaceutical companies remained consistent from 2007 to 2011 (Fig. 2, right panel).

TABLE 1. NUMBER OF DRUG CANDIDATES THAT WERE CREATED IN-HOUSE AND ACQUIRED FROM OUTSIDE ORGANIZATIONS BY JAPANESE PHARMACEUTICAL COMPANIES (1983 TO 2012)

	Launch	Failure				On-going				
		PC	Ph.1	Ph.2	Ph.3	PC	Ph.1	Ph.2	Ph.3	Total
In-house	251	1163	208	364	124	319	87	97	48	2661
% of total	9%	44%	8%	14%	5%	12%	3%	4%	2%	100%
Acquisition	362	72	28	111	54	26	9	65	66	793
% of total	46%	9%	4%	14%	7%	3%	1%	8%	8%	100%

PC: pre-clinical, Ph.: phase

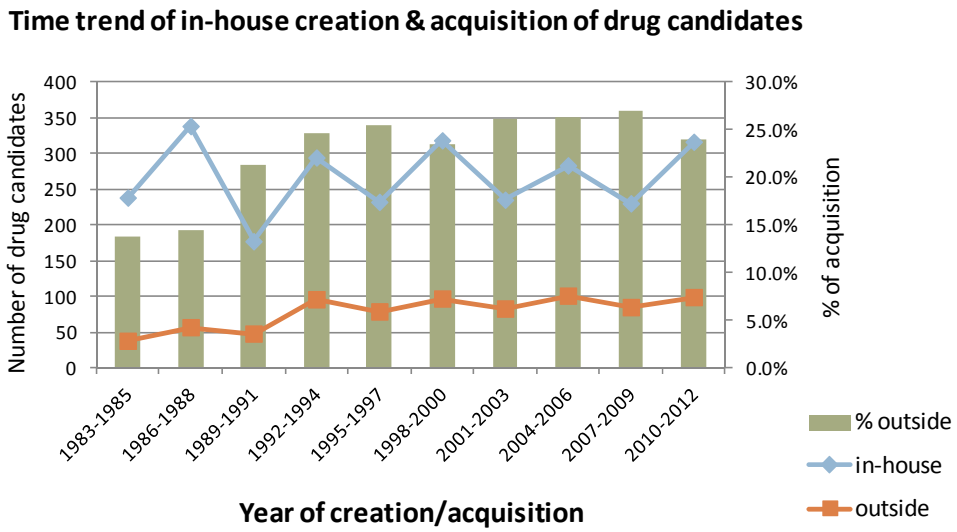

Fig. 1. Time trend of the number of internally-created and acquired drug candidates in Japanese pharmaceutical companies (1983 to 2012)

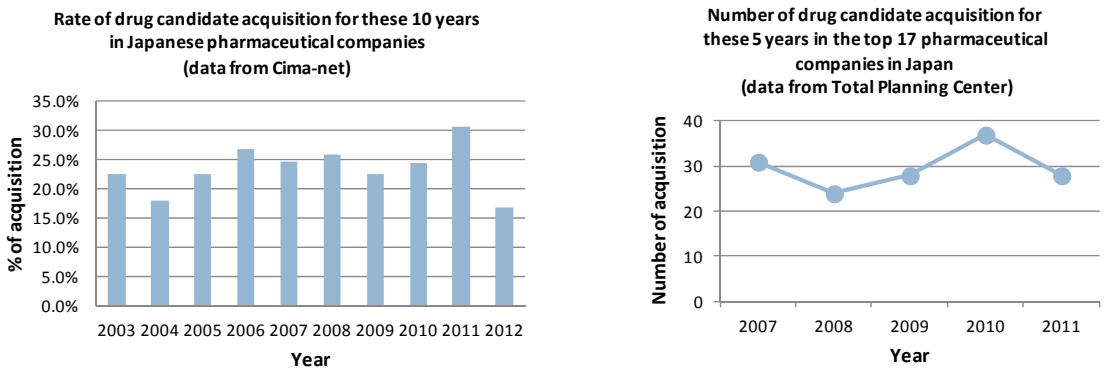

Fig. 2. Recent drug candidate acquisitions in Japanese pharmaceutical companies confirmed by two different sources

B. Clinical development stages of drug candidate acquisition in the Japanese pharmaceutical industry

As shown in Table 2, the most popular stage at which drug candidates were acquired was the pre-clinical stage, which accounted for 37.8% of acquired compounds. Interestingly, nearly one-fourth of acquired drug candidates were acquired for the purpose of being developed in other countries and/or for other indications after launched in at least one country and/or indication. The combined number of acquired drug candidates at phase 3 and at launch corresponded to the number of drug candidates acquired in the pre-clinical stage.

Fig. 3 indicates the time trend of the distribution of clinical development stages at which acquisition was conducted. Most of the drug candidate acquisitions were conducted at the preclinical stage during the 1980s. Then, starting in the 1990s, late-stage drug candidate acquisition continued to increase and has dominated in recent years. On the other hand, preclinical-stage acquisition has recently become inactive (Fig. 3).

TABLE 2. DISTRIBUTION OF CLINICAL DEVELOPMENT STAGES AT WHICH DRUG CANDIDATES WERE ACQUIRED.

	Pre-clinical	Phase 1	Phase 2	Phase 3	Launch*
# of projects	296	54	141	90	202
% of total	37.8%	6.9%	18.0%	11.5%	25.8%

*launched in at lease one country and/or for at lease one indication

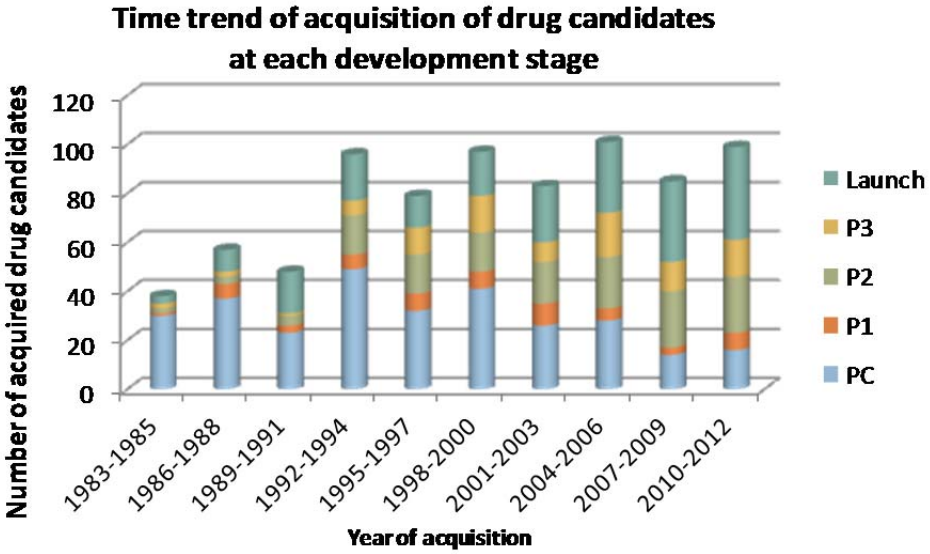

Fig. 3. Time trend of distribution of clinical development stages at which drug candidates were acquired.

C. Therapeutic area distribution in drug candidate acquisition

We investigated the distribution of therapeutic areas in the drug candidates acquired by Japanese pharmaceutical companies from 1983 to 2012. The most active therapeutic area for drug candidate acquisition was oncology, followed by inflammation and allergy, cardiovascular, central nerves system, metabolic and infection (Fig. 4).

To see if pharmaceutical companies use different therapeutic area strategies for in-house creation and acquisition of drug candidates, we conducted a statistical comparison of the therapeutic area distribution between the two categories in the selected Japanese pharmaceutical companies. To obtain large enough samples of drug candidates for the comparison, we selected relatively large Japanese pharmaceutical companies that were listed in the top 35 of globally ranked pharmaceutical sales in 2012 (http://www.utobrain.co.jp/news/20130624.shtml). Among them, we omitted the companies that were recently established by merger (i.e., DaiichiSankyo, Astellas, TanabeMitsubishi) because their strategies are based on the sum of two different companies' strategies. The analysis of the remaining four companies (Takeda, Eisai, Otsuka, Chugai) showed that there was no statistically significant difference in therapeutic area distribution between internally-created and acquired drug candidates in all of the four companies (Table 3).

Null hypothesis: No correlation between the origin of drug candidates (in-house or acquired) and the distribution of therapeutic area (infection, oncology, inflammation & allergy, metabolic, endocrine, hematology, cardiovascular, respiratory, digestive, central nervous system, sensory, urogenital, dermatology, others).

Null hypothesis was not rejected ($P < 0.10$).

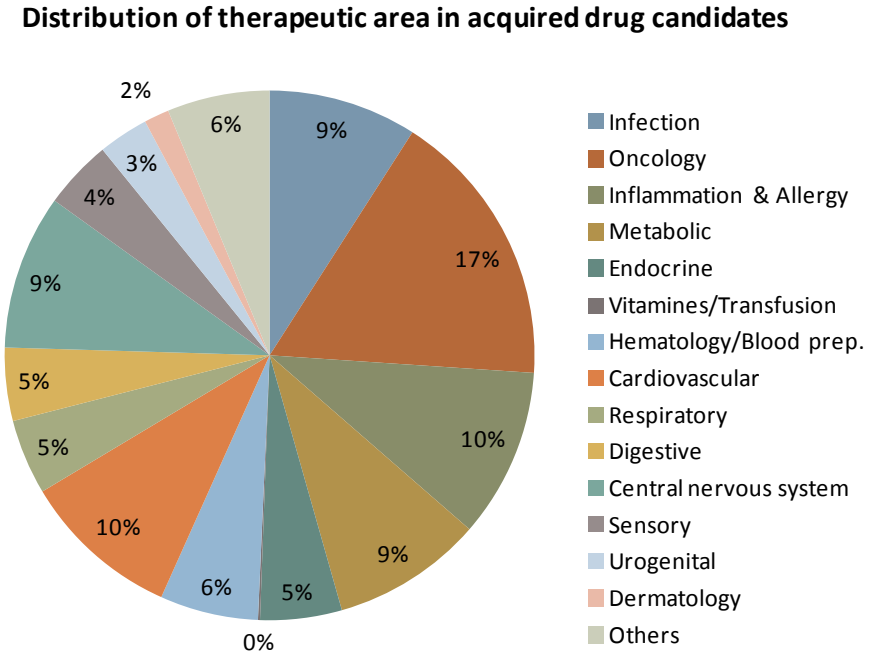

Fig. 4. Therapeutic area distribution of drug candidates acquired by Japanese pharmaceutical companies from 1983 to 2012

TABLE 3. CHI-SQUARE ANALYSIS OF THERAPEUTIC AREA DISTRIBUTION BETWEEN THE DRUG CANDIDATES CREATED AND ACQUIRED BY THE FOUR JAPANESE PHARMACEUTICAL COMPANIES FROM 1983 TO 2012.

Company	*P* -value by chi-square analysis
Takeda	0.1155
Eisai	0.7709
Otsuka	0.8597
Chugai	0.5382

V. DISCUSSION AND CONCLUSION

Our study indicated that Japanese pharmaceutical companies acquired approximately one-fourth of their clinically-developed drug candidates from outside organizations over the past 30 years. As acquired drug candidates already pass the clinical development stages earlier than the acquisition stage, the launch rate of the acquired drug candidates was higher (46%) than that of in-house projects (9%) that started from pre-clinical stage. These data suggest that Japanese pharmaceutical companies have largely used drug candidate acquisition as a risk-mitigating strategy to overcome the high attrition rate of in-house projects in clinical development and supplement product pipelines.

The time trend analysis revealed that drug candidate acquisition was prevalent in the 1980s, increased in the 1990s and has been steady during the last 20 years. Because drug candidate acquisition is one of the most important reasons of OI for Japanese pharmaceutical companies [14], it was unexpected that our analysis from three different sources consistently showed no recent increase of drug candidate acquisition, although the literature does note that OI strategy is becoming an emerging trend in Japanese pharmaceutical industry [13][24]. Our analysis based on the comprehensive data collection of clinically developed compounds does not support the results obtained from the survey and case analysis. We concluded that drug candidate acquisition has been broadly conducted during the past 30 years (especially from the 1990s onward) and has contributed significantly to new product launches within the Japanese pharmaceutical industry. At least in terms of drug candidate acquisition, OI is an established practice and not simply a recent trend. One possible reason for the discrepancy between current literature and our study is that our analysis focuses only on drug candidate acquisition. Although drug candidate acquisition is the most important reason for openness in the Japanese pharmaceutical industry [14], introduction of new technologies for drug research [14] and U-I collaboration at early-stage research [24] are also important elements of OI. Our previous study revealed that the number of drug discovery projects involving U-I collaboration also has not increased in recent years [17]. It is possible that the recent advocacy of OI in the Japanese pharmaceutical industry focuses on collaborations other than drug discovery and candidate acquisition.

An implication for managerial practice from the above time trend analysis is that Japanese pharmaceutical companies should leverage drug candidate acquisition, which did not increase for these 20 years, more aggressively. Because about half of new drugs have been produced by small biotechnology start-ups [12] and the pharmaceutical companies that were more enthusiastic about acquisition generated higher earnings [21], Japanese pharmaceutical companies should take the strategic shift from autarkic R&D to externally acquisition model more proactively. As shown in our analysis, drug candidate acquisition has been a useful strategy for Japanese pharmaceutical companies to complement their project portfolios; therefore, the companies should view this advantage more positively.

The changes in the clinical development stages at which drug candidates were acquired reflect a strategic shift within the Japanese pharmaceutical companies. In the 1980s, drug candidate acquisition in the pre-clinical stage was dominant; Japanese pharmaceutical companies acquired drug candidates primarily to complement their development pipelines. Starting in the 1990s, drug candidate acquisition in the late development stage or even acquisition of launched compounds became dominant. Companies shifted their acquisition strategies to expand their product portfolio by increasing late-stage deals rather than acquiring early-stage compounds in the 1990s. This strategic change coincides with the same period that saw the efficiency of new drug development (launch of new chemical entity per R&D expenditure) start to decline [23]. Therefore, it is speculated that Japanese pharmaceutical companies leveraged relatively low-risk late-stage drug candidate acquisition to compensate for the lack of product pipelines due to the decreased productivity of internal drug discovery and development.

An implication for managerial practice obtained from the analysis of the acquisition stage is that Japanese pharmaceutical companies should increase early-stage compound acquisition. In the large multinational pharmaceutical companies, the acquisition of late-stage drug candidates has also been dominant; however, early-stage deals bean to increase in the mid 2000s due to the scarcity and high cost of late-stage compounds [11][18]. Because of the end of the blockbuster model and the increasing demand for personalized medicines, Japanese pharmaceutical companies need to diversify their development pipelines [5][25]. For that purpose, relatively low cost early-stage acquisition could be increasingly leveraged.

In our results, the most popular therapeutic area in drug candidate acquisition was oncology. According to the analysis of the world's 40 largest pharmaceutical companies, 28% of all collaborative activity has focused on oncology [11], suggesting that oncology is the hottest therapeutic field in compound hunting. Our statistical analysis indicates that there was no significant difference of therapeutic area distribution between in-house-origin and acquired drug candidates in any of the four companies selected, implying that drug candidate acquisition has been utilized to reinforce internal R&D. An implication for managerial practice obtained from the analysis of therapeutic area is that Japanese pharmaceutical companies should enhance the acquisition of drug candidates in the therapeutic areas that are different from those areas covered by in-house research projects. It takes a long time to strengthen in-house research capability; therefore, drug candidate acquisition could be a good strategic option for companies seeking to increase their project portfolios quickly in the therapeutic areas for which they do not have the internal capability. To establish broader

product portfolios, it may be important for companies to acquire drug candidates in the therapeutic areas that internal R&D does not focus on.

Our study addresses only the drug candidate acquisition cases where individual compounds are introduced by in-licensing or co-development. In large multinational pharmaceutical firms, M&A is one of the major ways to acquire drug candidates. Approximately half of the drug candidates from external sources are introduced by the acquisition of entire companies in those firms [21]. In the Japanese pharmaceutical industry, company mergers began to happen in the mid 2000s (e.g., Astellas in 2005, Dainippon Sumitomo in 2005, DaiichiSankyo in 2007), and more recently, acquisition of overseas pharmaceutical companies is increasing (e.g., acquisition of Millennium in 2008 and Nycomed in 2011 by Takeda). To view the entirety of drug candidate acquisition within the Japanese pharmaceutical industry comprehensively, robust studies examining M&A will be needed in the future.

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