Analysis of the current status of orphan drug development and consideration of measures for its promotion

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Abstract

Orphan drugs have become a key area of focus in drug development for resolving unmet medical needs. The Orphan Drug Act in the United States was enacted in 1983, followed by similar legislations in Japan, the European Union, and several other countries with the aim to promote the development of orphan drugs. These legislations provide regulatory and financial supports and incentives to the parties who develop orphan drugs. Despite these efforts, the number of approved orphan drugs is still limited.

In this study, a quantitative review of all orphan drug designations and approvals since the implementation of orphan drug legislations in the key three regions, Japan, the United States and European Union was conducted. It also identified and reviewed 'commonly designated' drugs across the regions. Out of nearly 5,000 designations, approximately 800 designations were common among the United States, European Union and/or Japan. Regional similarities, differences and trends were identified. The delayed marketing approvals of orphan drugs in Japan were noteworthy, which was 41 months behind the US approvals.

This study also quantitatively reviewed Japanese major pharmaceutical companies' licensing/collaborations with the academia. Recent news releases were analyzed to identify the current situation and trend in Japanese academia-industry collaboration. Novel technology and development candidates were found as the area of collaboration to be enhanced. Limited collaborations between Japanese academia and industry were

identified whilst Japanese academia has been the pioneers in cutting edge science.

These two analyses revealed the bottlenecks in the orphan drug development in Japan from agency-industry and academia-industry collaboration perspectives. Revision of the orphan drug regulation on designation and applicant criteria, and initiation of close collaboration between academia and industry from the early phase of research were considered to be effective measures for the promotion of orphan drug development in Japan. They will enable the key stakeholders, academia, agency and industry, to have more substantial contributions to orphan drug development and to patients with rare diseases.

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Abbreviations

AMD	Age-related Macular Degeneration
ATC	Anatomical Therapeutic Chemical Classification System
EU	European Union
FDA	US Food and Drug Administration
iPS	induced Pluripotent Stem cells
NPO	Non-Profit Organization
NTD	Neglected Tropical Disease
PMDA	Pharmaceuticals and Medical Devices Agency
RPE	Retinal Pigment Epithelium
US	The United States of America
WHO	World Health Organization

1. Introduction

Despite the fact that rare diseases are often chronically debilitating, life-threatening, and/or life-limiting, the relatively small number of patients affected by such diseases reduces incentive for the pharmaceutical industry to develop drugs to treat them. To date, nearly 7,000 of these rare diseases have been identified, many of which have a genetic basis and affect patients early in childhood [1]. This represents substantial unmet medical and social needs. Technological advances such as phenotypic assays, target-based approaches and biologic strategies have increased the number of orphan drugs as is often observed in oncology and metabolic diseases [2-4]. Furthermore, a recent trend to "re-purpose" commercialized products for other rare diseases also encourages the industry to develop orphan drugs [5].

The development of orphan drugs represents a challenge for the pharmaceutical industry, as the limited number of patients suffering from rare diseases necessarily means lower profit margins. In 1983, the US government implemented the Orphan Drug Act to encourage the pharmaceutical industry to increase and accelerate the development of orphan drugs, with similar mechanisms implemented in Japan in 1993 and the European Union (EU) in 2000. Although the eligibility for the orphan drug designation differs slightly depending on the legislation and policies adopted by each region, they are similar in that they mainly focus on the number of patients along with the likelihood the product will have utility in the disease [6].

Rare diseases represent a key area of focus in drug development, with approval rates

in 2014 for orphan new active substances (NASs) in each region as follows: US, 47%; EU, 43%; and Japan, 37% [7]. Countries in Asia, Oceania, and South America, such as Australia, Mexico, Argentina, Chile, Columbia, Taiwan and Korea, have implemented or are planning to implement orphan drug mechanisms similar to those in the US, the EU or Japan in order to promote orphan drug development [8,9]. A number of initiatives and programs have also been implemented by non-industry organizations specifically for rare diseases, or for various disorders including rare diseases, such as the Drugs for Neglected Diseases initiative by the nonprofit organization Doctors Without Borders, and Therapeutics for Rare and Neglected Diseases and the Rare Diseases Clinical Research Network by the National Institutes of Health [10-12]. Organizations of all types—governmental, commercial, and academic—are now collaborating in orphan drug development to ensure that more of these medicines reach patients as swiftly as possible. Despite these governmental and non-governmental efforts, the number of approved orphan drugs is still limited. Approximately 500 marketing approvals alone have been achieved even in the United States which firstly enacted orphan legislation [13].

The aim of our research is to present a solution to the unanswered critical questions on orphan drugs; "How could the novel treatments for the rare diseases be conveyed to the patients faster?" and "How could the key stakeholders, academia, agency and industry, could collaborate more efficiently to convey treatments?" It is crucial for these key stakeholders to collaborate each other to convey novel treatments to the patients. Academia makes cutting edge researches on novel therapeutic targets and novel technologies. Industry bears the role for the realization and commercialization of novel treatments and technologies. Agency bears the role to aid the research and development

in the academia and the industry. Harmonized collaborative work among these parties could be the basis to convey novel treatments to the patients with rare diseases.

In this research, the way how to enhance the collaborative work among academia, agency and industry was investigated in addition to the analysis on current status on the orphan drug research and development.

2. Part 1

2.1 Background

Despite the fact that rare diseases are often chronically debilitating, life-threatening, and/or life-limiting, the relatively small number of patients affected by such diseases reduces incentive for the pharmaceutical industry to develop drugs to treat them. To date, nearly 7,000 of these rare diseases have been identified, many of which have a genetic basis and affect patients early in childhood. This represents substantial unmet medical and social needs.

In Part 1 of the research, "Orphan drug development and the regulatory environment in the US, EU and Japan (agency-industry collaboration)" was investigated to identify the current status of global orphan drug development, and to identify a solution to the enhancement in agency-industry collaborations. Current status of orphan drug designations and marketing approvals were analyzed using entire data from the US, EU and Japan. Furthermore, the trends and identified differences in orphan drug designations and marketing approvals among the US, the EU and Japan after the implementation of legislation are characterized by region. This was accomplished by analyzing the status of orphan drug designations and approvals based on the matched data across the three regions. Such a matched analysis using entire orphan designations and marketing approvals is the first attempted approach which enables us to analyze the regional difference quantitatively and thoroughly. We consider this approach to serve as a basis for future examination of measures to further optimize orphan drug development.

Several reviews of regulations and accumulated experience in specific regions have been conducted [14-16], and one study conducted a cross-regional comparison of orphan drug designations and approvals [6]. Another analysis used data from commercial databases, although the databases did not cover all regional designations [17]. However, as yet, no quantitative comparative study across regions has conducted a data-matched analysis of orphan drug designations and approvals among the USA, EU, and Japan.

Given that there still be significant unmet needs in the orphan drugs, and given that there have been limited researches to date on orphan drug development, we decided to make an attempt to firstly analyze current status of orphan drug development in a fully quantitative fashion.

2.2 Method

Lists of designated orphan drugs as of February 28, 2015 were obtained from the databases of the websites of the US FDA, the European Commission, and the National Institute of Biomedical Innovation in Japan [13,18,19].

All regional data were then entered into a spreadsheet and coded by drug type, applicant type, and therapeutic classification. Drug type was coded as either small molecule, biologic, nucleic acid/vector/cell/tissue, vaccine, or others. Chemicals, amino acids, and small peptides (<100 amino acids in length) were coded as small molecules. Antibodies, fusion proteins, and high-molecular-weight enzymes (>10 kD) were coded as biologics. Plasmids and vectors were coded as vectors, cells as cells, and tissue products as tissues. Vaccines for infectious disease prophylaxis, such as influenza vaccine, were coded as vaccines.

Applicant type was categorized based on the SCRIP 100 total revenue ranking in 2013 as in the top 1–10, 11–30, 31–50, 51–100, or 101+ companies in the pharmaceutical industry [20]. If an applicant is not from a pharmaceutical company but rather from an academic or research institution, they were categorized as academia/institution. Therapeutic classifications were assigned based on ATC codes, referencing existing medications and WHO guidelines [21].

First designation dates and approval dates were integrated into the spreadsheet if multiple dates were available for a single product, for reasons such as a change in

applicant in Japanese orphan designations. Numbers of indications per drug was determined based on the drug name. When the drug names in the orphan drug designations were the same, they were regarded as the same drug. In biologics and recombinant enzymes, the drugs were regarded as different drugs unless the brand name or other descriptions suggests their identity, because recombinant biologics or enzymes are not identical even when they have the same target molecules or substrates.

After the spreadsheet entry, data were matched by pairing drugs in each region with drugs in other regions as follows: integrated data were sorted by drug name, then, pairings were performed repeatedly based on the brand name, applicant name, and proposed indication to provide the best match. Databases such as Orphanet were also referenced to identify drug pairs [22].

Individual data were duplicated in the spreadsheet when the granularity for a specific indication differed between regions. For example, for a recombinant human factor VIIa, the proposed indication in the US was "hemophilia". In contrast, the indications are more granular in the EU, which are "hemophilia A" and "hemophilia B". In this case, the original US item was duplicated to make 2 complete pairs with the EU items in the dataset.

We ultimately obtained two datasets from the integrated spreadsheet: After pairing/matching designations among the US, EU and Japan, we obtained one integrated dataset. The first dataset is the entire dataset which includes all paired and unpaired data ("all data"), while the second includes only paired data with matches between either two

or all three regions ("matched data").

Descriptive statistics on drug type, applicant type, therapeutic classification and number of indications per drug were calculated for "all data", while the time difference for orphan drug designations and marketing approvals were compared using "matched data". Data in the US were used as references, and comparisons were made between the EU and the US, and between Japan and the US.

2.3 Result

2.3.1 Overview

From implementation of legislations up to February 28, 2015, the following numbers of orphan designations were identified in each region: 3,345 in the US, 1,146 in the EU, and 359 in Japan (Table 1). Of these designations, marketing approval was given to 496 products in the US, 87 in the EU, and 236 in Japan.

The US continues to have the most designations and the most approvals with 290 orphan drug designations and 40 approvals in 2014 alone. The EU ranked second for orphan drug designations, while Japan ranked second for approvals. Orphan drug designations and their marketing approvals in 2014 were 184 and 14, respectively, in the EU, and 38 and 14, respectively, in Japan. Taking into the account the fact that the EU had the legislation adopted the latest (in 2000), the EU has been rapidly and intensively focusing their attention on orphan drug designations.

The percentage of successful marketing approvals to orphan drug designations were identified in each region: 14.6% in the US, 7.6% in the EU, and 64.8% in Japan. Japan had the highest ratio over 60 % while the US and EU had approximately 10 % ratio.

Matching each drug yielded the following orphan drug designations: 3,390 in the US, 1,146 in the EU, and 364 in Japan (Table 1). Annual designations since the implementation of orphan drug legislation for each region are shown in Figure 1.

Table 1 Type of applicant, therapeutic classification, and type of drug of the designated orphan drugs.

	US	EU	JP
Original data from agencies			
Data collection period	1983–February 28, 2015	2000–February 28, 2015	1993–February 28, 2015
Number of orphan drug designations	3,345	1,146	359
Number of marketing approvals of designated orphan drugs	496	87	236
Dataset after integration/matching (all data)			
Number of orphan drug designations	3,390	1,146	364
Number receiving marketing approval	496	87	236
Approval/designation ratio (%)	*14.6*	*7.6*	*64.8*
Applicant type (%)			
Top 1–10[a]	15.4	9.9	34.9
Top 11–30	7.9	5.2	15.9
Top 31–50	4.3	4.6	14.0
Top 51–100	3.1	4.2	3.8
Top 101+	64.5	69.6	31.3
Academia/Institutions	4.7	6.2	0.0
Others	0.1	0.2	0.0
Total	100.0	100.0	100.0
Therapeutic classification (ATC code) (%)			
A (Alimentary tract and metabolism)	10.4	15.8	11.3
B (Blood and blood-forming organs)	7.0	5.7	7.4
C (Cardiovascular system)	3.5	3.3	5.5
D (Dermatological drugs)	1.7	1.7	0.3
G (Genitourinary system and reproductive hormones)	1.7	0.9	2.2

H (Systemic hormonal preparations, excluding reproductive hormones and insulin)	1.6	2.1	1.9
J (Anti-infective products for systemic use)	6.8	4.4	16.5
L (Antineoplastic and immunomodulating agents)	40.4	40.8	31.0
M (Musculoskeletal system)	3.7	4.9	3.6
N (Nervous system)	8.8	7.2	10.7
P (Antiparasitic products, insecticides, and repellents)	1.8	0.7	1.4
R (Respiratory system)	4.4	6.3	1.4
S (Sensory organs)	2.9	4.7	3.6
V (Various ATC structures)	4.2	1.7	2.7
Others	1.2	0.0	0.5
Total	100.0	100.0	100.0
Drug type (%)			
Small molecules	59.5	56.0	63.5
Biologics	27.3	25.5	31.0
Nucleic acids/vectors/cells/tissues	9.4	17.1	1.1
Vaccines	0.7	0.3	3.8
Others	3.2	1.0	0.5
Total	100.0	100.0	100.0
Number of indications per drug (%)			
1 indication	74.0	81.1	86.2
2 indications	15.4	13.0	9.1
3 indications	5.3	3.5	2.7
4 or more indications	5.3	2.4	2.0
Total	100.0	100.0	100.0

[a] Categorized by revenue ranking in the 2013 SCRIP 100

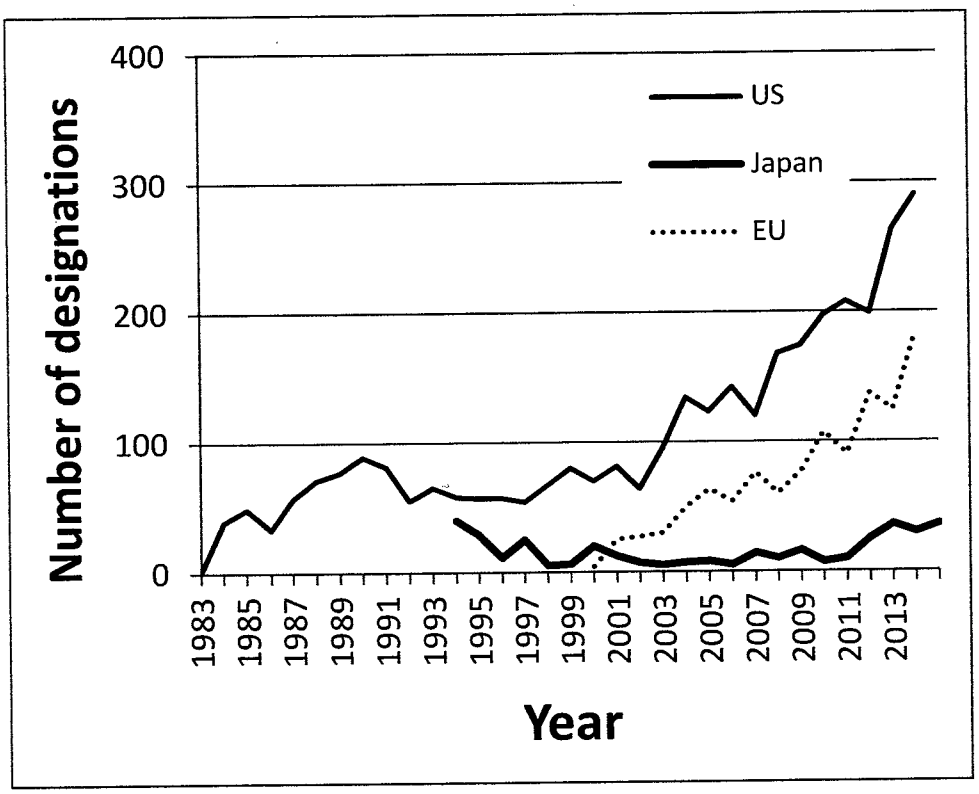


Figure 1 Number of orphan drug designations over time in the US, EU and Japan (all data).

Number of orphan drug designations

The number of orphan drug designations has steadily increased in the US, the EU, and Japan since introduction of relevant legislations. The number of designations increased over time, with the following numbers of products in each region designated as orphan drugs in 2014: 290 in the US, 184 in the EU, and 36 in Japan.

Number of marketing approvals

The integrated single database identified 496 approvals in the US, 87 in the EU, and 236 in Japan since the introduction of relevant legislation, with numbers of annual orphan drug approvals steadily increasing across all three regions. Under Japanese regulations, only drugs with a high chance of approval may be designated as orphan drugs, a fairly strict condition which may function as a gatekeeper for the selection of highly approvable drugs in Japan. This possibly accounts for the high approval/designation ratio in Japan. In contrast, the US and EU legislations are providing the applicant with more opportunities for orphan drug designations and their benefits from earlier phases of development regardless of the future approvability. The benefit and risk in each approach should be further investigated.

2.3.2 Analysis of all the designated orphan drugs in US, EU or Japan (all data)

Applicant type

The applicant type, therapeutic classification, and drug type for orphan designation are summarized in Table 1. Regarding applicant type, no marked differences were noted between the US and the EU. However, of note, large pharmaceutical companies with revenue ranking in the top ten globally accounted for 34.8% of applicants in Japan but only 15.4% in the US and 9.9% in the EU. Further, while academia- or institution-based designations were observed in the US (4.7%) and the EU (6.2%), there were none in Japan.

Therapeutic classification

Regarding therapeutic classification, ATC Code L (oncology and immunomodulatory drugs) accounted for 30% to 40% of total designations across the three regions. While no marked differences were noted in overall classification between the US and the EU, the percentage of ATC Code J (infectious diseases) was higher in Japan than in the US or EU.

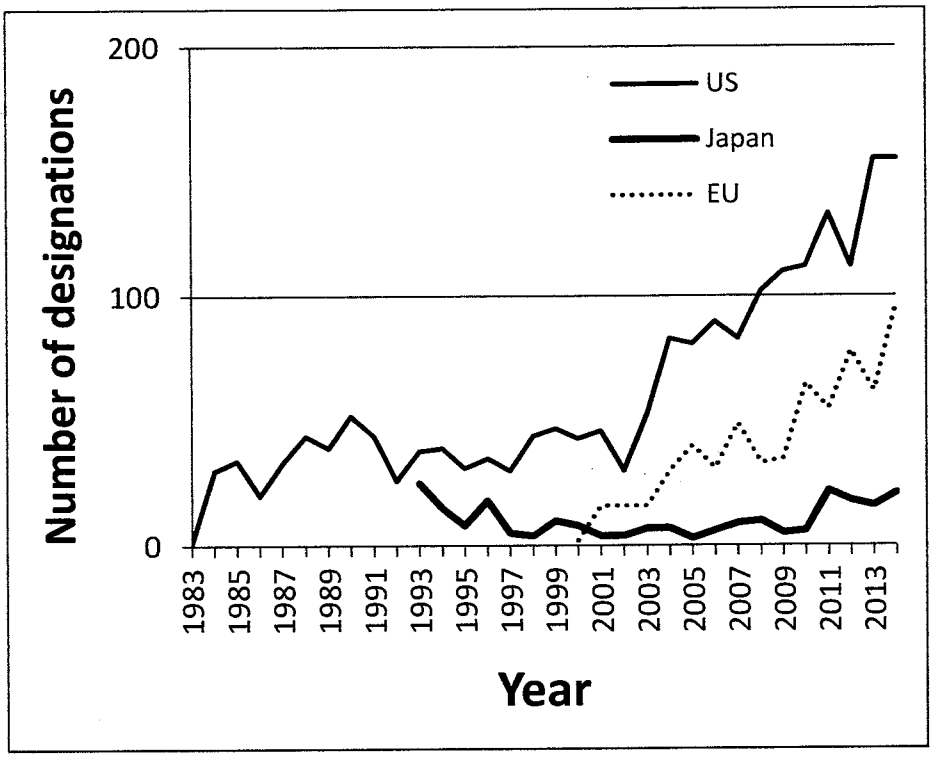
Drug type

Regarding drug type, small molecules accounted for the majority of designations, up to approximately 60%. Vaccines were more prevalent in Japan than in the US or the EU. At 3.8% of designations in Japan, vaccines represent one of the major classification groups in this country, compared to 0.7% in the US and 0.3% in the EU. This difference is attributable to the Japan-specific scope for orphan designation that covers vaccines

for unrealized infectious diseases, such as pandemics [23].

New modalities, such as nucleic acids, vectors, cells, and tissues, have steadily increased their prevalence in the US and the EU, as shown in Figure 2. Cell and tissue products in particular were more dominant in the EU than in the US and Japan. In Japan, JR-031 (mesenchymal stem cell) and NPR-01 (adipose-derived stem cell) alone were listed as orphan drugs in the original website data. Additional investigation identified limited designations for tissue or cell-sheet therapy not as drugs but as medical devices, suggesting generally limited orphan designations for cell and tissue products in Japan [24].

(a)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Number of designations
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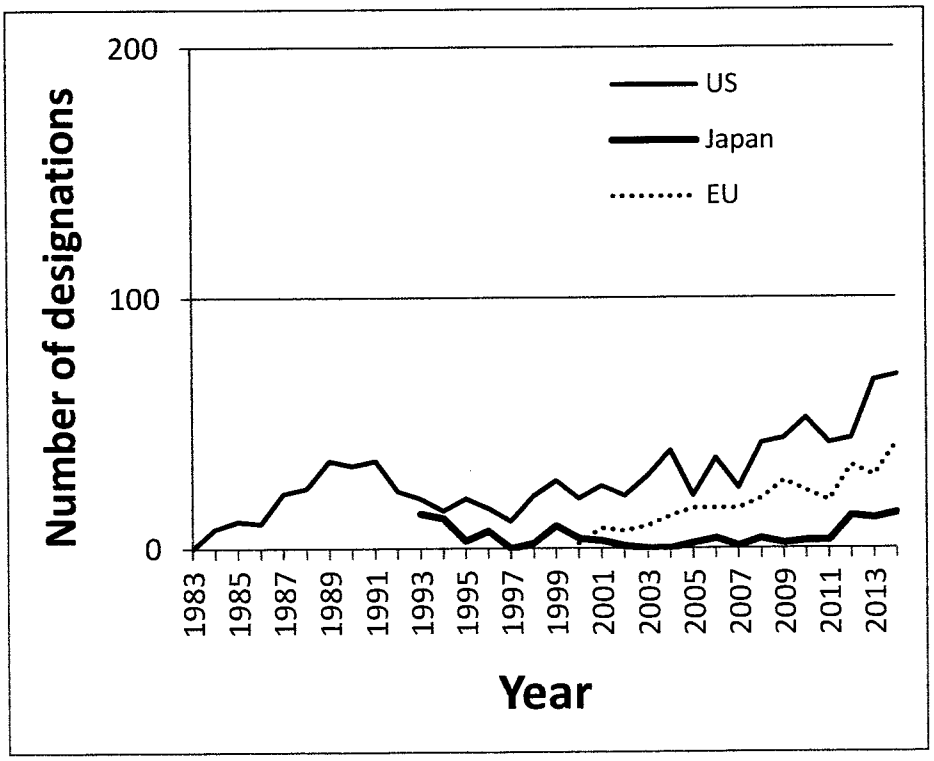
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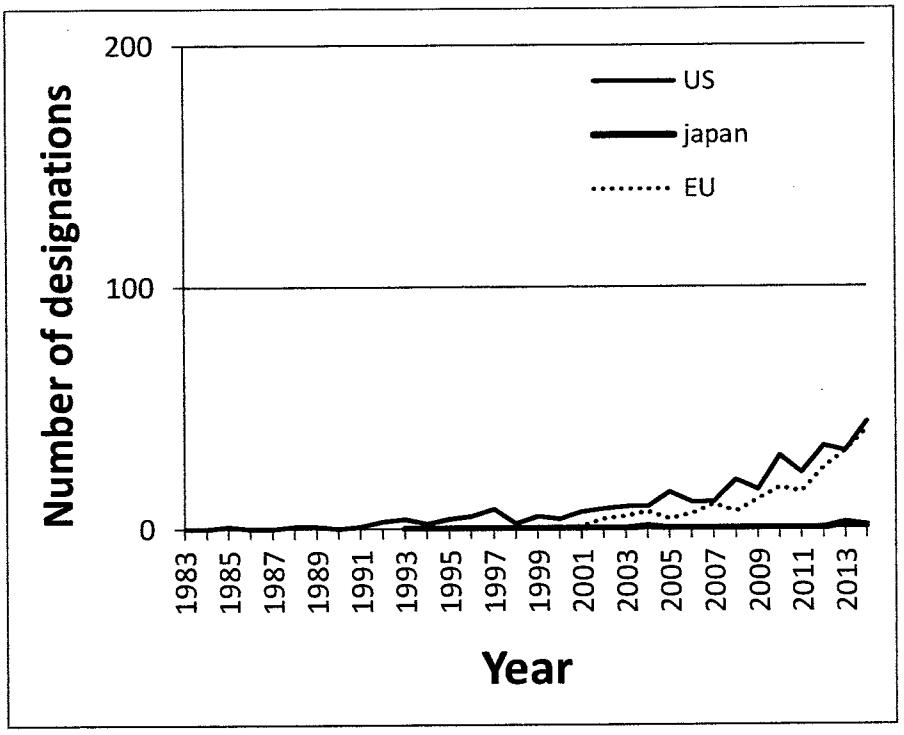


Figure 2 Number of orphan drug designations for small molecules (Figure 2(a)), biologics (Figure 2(b)), and new modalities (Figure 2(c)) (nucleic acid, vector, cell, and tissue products) over time in the US, EU and Japan (all data).

Number of indications per each product

The number of indications per each drug was assessed to identify whether single or multiple indications are pursued in orphan drug development. As presented in Table 1, single indication accounted for the largest segment of all orphan designated drugs across regions. Japan had the highest rate of single indication at 86.2 % while the US and the EU had 74.0 % and 81.1 %, respectively.

2.3.3 Analysis of commonly designated orphan drugs in US/EU or US/Japan (matched data)

Figure 3 summarizes the status of orphan drug designations by region and across regions in a Venn diagram. "Matched data" used in our analysis are presented in Figure 3 with highlight with the underline (745 products in total as the sum of 134, 57 and 554 products). Considerable overlaps were identified across the regions. Fifty three percent of the EU designations were also designated in the US (611/1146 drugs). Fifty two percent of Japanese designations have been also designated in the US (191/364 drugs).

A similar finding was observed in the approvals of orphan drugs (Venn diagram not presented). Forty nine percent of the EU approvals were also approved in the US (43/87 drugs).Forty one percent of Japanese approvals have been also approved in the US (96/236 drugs).

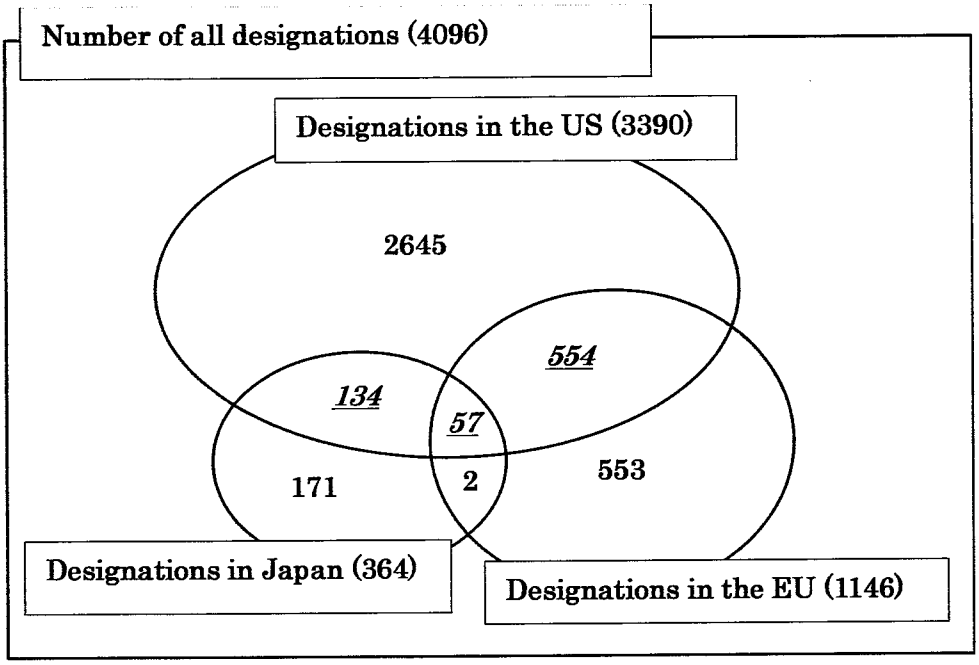


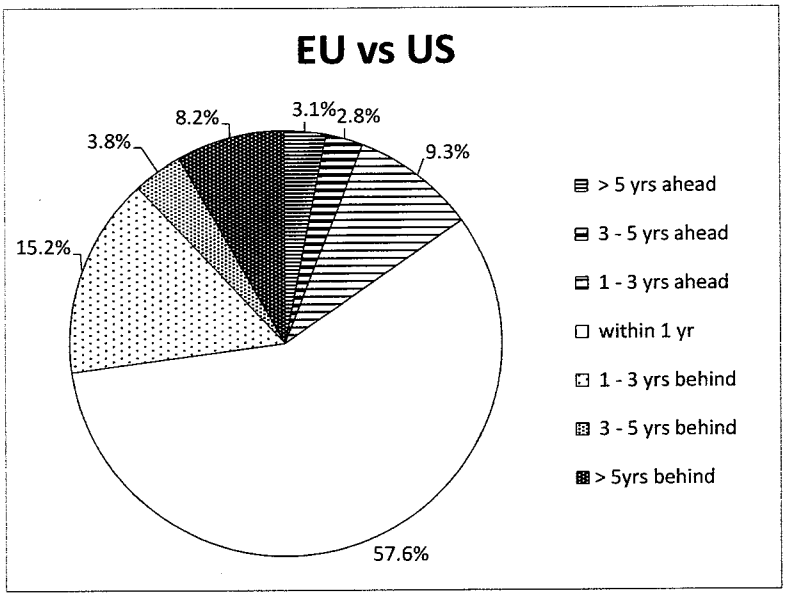
Figure 3 Venn diagram for orphan drug designations in the US, EU and Japan. Underlined data are the "matched data" which consists of commonly designated products in 2 or 3 regions of the US, EU or Japan.

Time difference in the orphan drug designations

Figure 4 shows the distribution of time difference in orphan drug designations either in the EU or Japan compared to the US. In the EU, 57.6% (352/611) of designations were made within 1 year of designation in the US, while only 14.1% (27/191) of drugs in Japan were designated as orphans within that same window. The median designation time difference in the EU was 3 months after the designation in the US (Q1, -3 months, Q3, 14 months), while that in Japan was 40 months post-US (Q1, 11 months, Q3, 91 months). No remarkable trends such as decreased or increased time difference compared with US designation were noted for either the EU or Japan. In 2014, median time

difference was 3 months (Q1, -1 months, Q3, 11 months) for 85 matched designations in the EU and 25 months (Q1, 10 months, Q3, 74 months) for 27 matched designations in Japan, compared with the US.

(a)



(b)

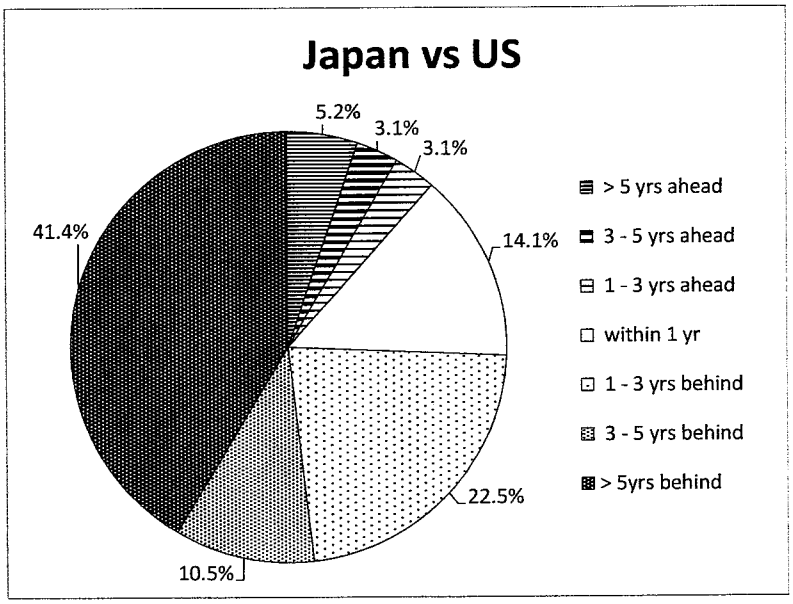


Figure 4 Time difference for orphan drug designations between the EU and the US (Figure 4(a)) and between Japan and the US (Figure 4(b)).

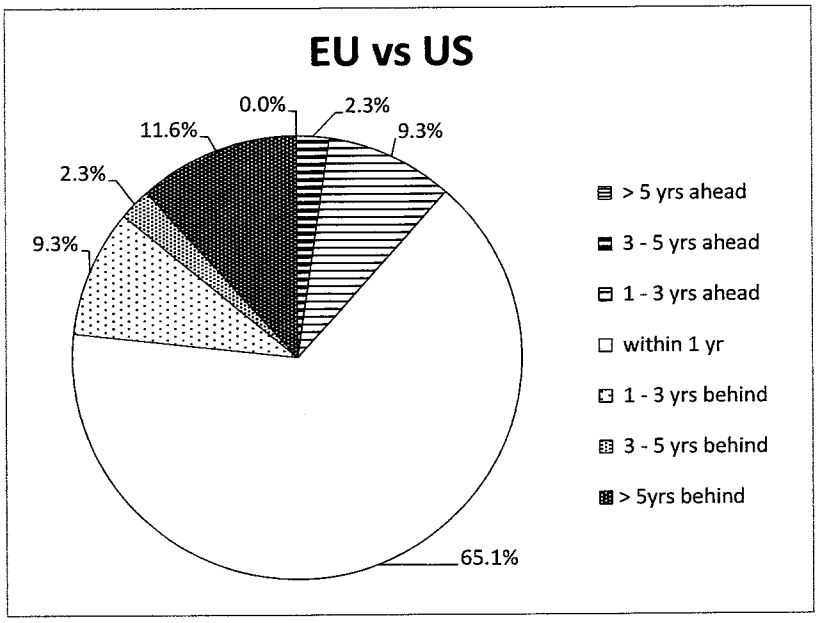
Designation dates were compared in the commonly designated products in the US and EU. The US designation dates were used as the comparator/baseline. In the same way, designation dates were compared between Japan and the US.

Time difference in the marketing approvals

Similar analyses were performed for time difference in marketing approval for orphan drugs. In the EU, 65.1% (28/43) of approvals were made within 1 year of approval in the US, while only 14.6% (14/96) of orphan drugs in Japan were approved within that same window (Figure 5). The median approval time difference in the EU was 6 months after approval in the US (Q1, 2 months, Q3, 12 months), while that in Japan was 41 months post-US approval (Q1, 18 months, Q3, 87 months). No remarkable trends such as chronologically decreased or increased time difference compared with US approval were noted for either the EU or Japan (Figure 6).

We also analyzed the time to approval from orphan drug designation between the regional orphan designation and its regional marketing approval in each region. For US-EU common products, the median time to marketing approval from orphan designation were 42 and 45 months in the US and EU, respectively (n=43). For US-Japan common products, they were 33.5 and 27 months in the US and Japan, respectively (n=96). Japan had a relatively shorter time to approval from designation while the EU had a similar time period compared with the US, suggesting late designation due to the Japan-specific condition requiring "high possibility of development" for orphan drug designations.

(a)



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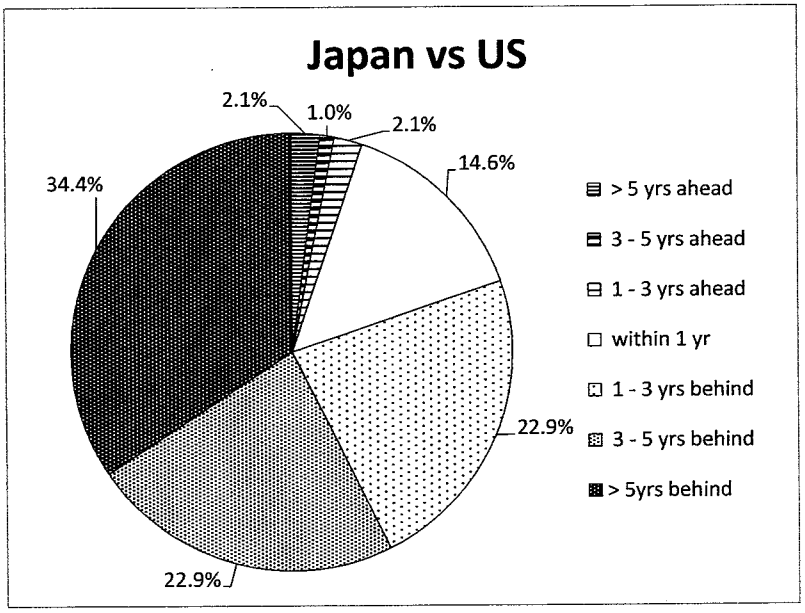
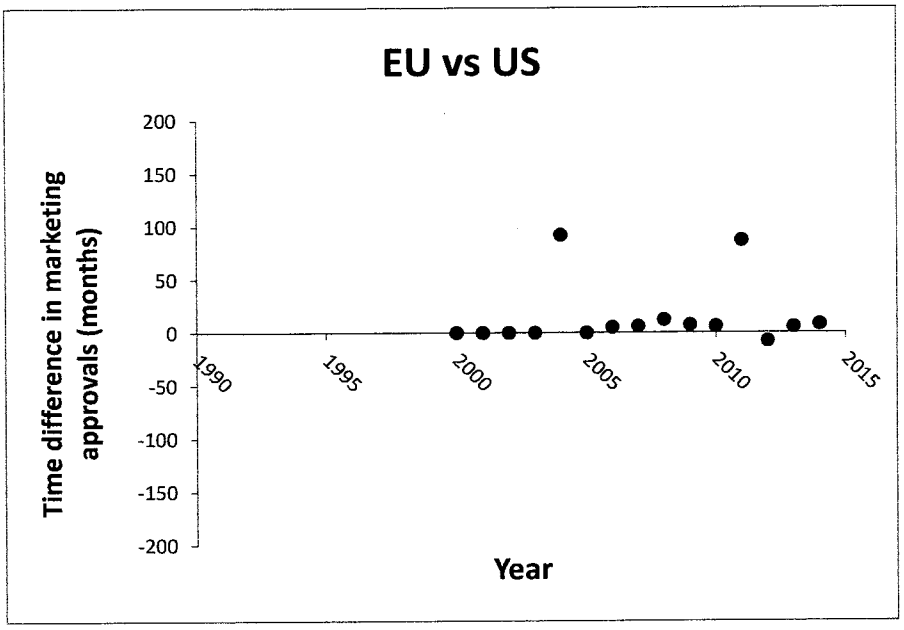


Figure 5 Time difference for marketing approvals between the EU and the US (Figure 5(a)) and between Japan and the US (Figure 5(b)). Marketing approval dates were compared in the commonly approved products in the US and EU. The US approval dates were used as the comparator/baseline. In the same way, approval dates were compared between Japan and the US.

(a)



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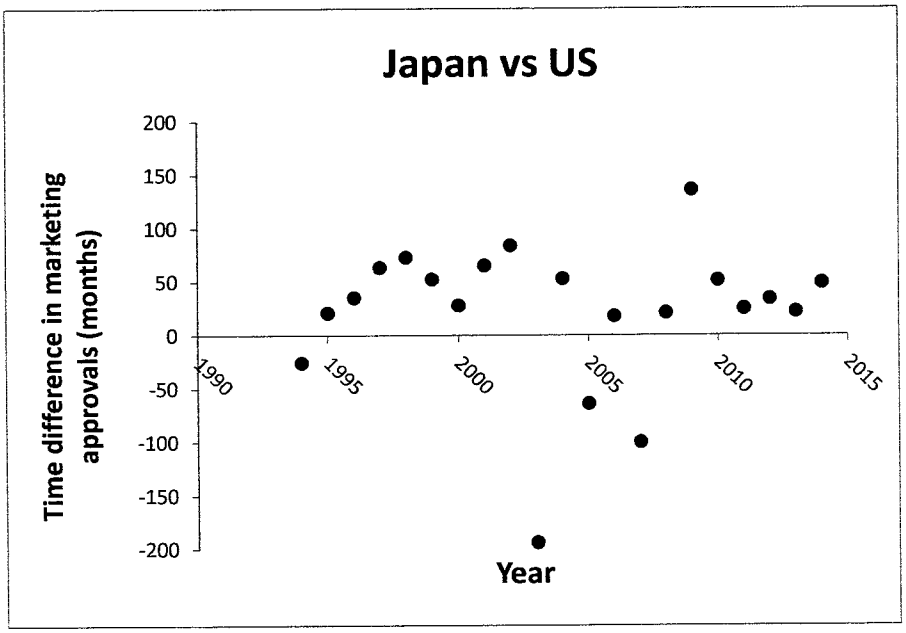


Figure 6 Chronological median time difference in marketing approvals between the EU and the US (Figure 6(a)) and between Japan and the US (Figure 6(b)).

2.4 Discussion

Continuously increasing number of orphan drug designations suggests that orphan drug legislation remains a critical part of the drug development process. Each regulatory body has implemented or is planning to implement expedited mechanisms to deliver new drugs to patients as quickly as possible while their scope is not limited to orphan drugs but includes any drugs which meet their criteria. In the US, the breakthrough designation mechanism was implemented to support existing expedited pathways such as accelerated approvals and fast track. In the EU, existing guidelines on accelerated assessment and conditional marketing authorization are undergoing revision. Priority Medicines (PRIME) scheme has just been launched on March 7, 2016 [25]. The Japanese version of the breakthrough designation, Sakigake, was recently initiated as a pilot program in 2015 [26]. In addition, the Usage of Unapproved Drugs Review Committee was established in Japan in 2005 to address the issue of unapproved drugs to treat rare diseases and to provide patients with regulatory and financial safety nets [27]. The pharmaceutical industry is currently investigating the best combinations of these mechanisms to obtain approval of new drugs that will more efficiently address unmet medical needs [7].

Despite the introduction of various priority/expedited programs for solely orphan diseases or for various maladies including orphan diseases, orphan drug legislation remains an invaluable and irreplaceable mechanism. Designation as an orphan drug is unique with its criteria primarily based on size of the patient population along with the likelihood the product will have utility in the disease.

Improvements in understanding of the biology and genetics of rare diseases and segmentation of established diseases (e.g., "precision medicine") has resulted in efficacy gradation, with greater efficacy being demonstrated in certain sub-populations than in more general populations, thereby reducing the primary target population. The steady increase of designation as an orphan drug in the US and EU has coincided with a shift to a more segmented treatment paradigm in research and development for these diseases.

This increase will also benefit applicants with respect to expedited pre-approval timelines, frequency of advice from regulators, financial assistance, and extended marketing exclusivity. While blockbuster drugs are always in demand, niche-busters catering to a more specific population have also emerged [28]. Orphan drug legislation is therefore considered to remain a critical part of the drug development paths.

Our finding of 41 months of time difference in marketing approvals of orphan drugs in Japan compared with the US is noteworthy. The Pharmaceutical and Medical Device Agency (PMDA) has indicated that so-called "drug lags for new molecular entities" became less than or approximately 1 year in 2012 and 2013, and such a lag has been solved [29]. According to our analysis on the time to approval from orphan drug designation between the regional orphan designation and its regional marketing approval, Japan had a relatively shorter time to approval from designation compared with the US. (33.5 and 27 months in the US and Japan, respectively (n=96)). The difference between Japan and the US was merely 6.5 months. This suggests the delayed

timing in orphan drug designation is one of the key factors that delays marketing approvals in Japan. This late designation can attributable to the Japan-specific condition requiring "high possibility of development" for orphan drug designations.

The overly long designation time difference noted in Japan may also be due to the source of orphan drugs. In Japan, 34.9% of designations were obtained from pharmaceutical companies with revenue size ranking in the top 10 in the world; in contrast, only 15.4% of designations in the US and 9.9% in the EU came from such companies. This finding indicates that Japanese large pharmaceutical companies are developing orphan drugs after initial approval or at a later stage of development than in the US. Japanese regulations do not expect to receive applications for orphan drug designations from academic researchers, limiting such applications to commercial companies that will be future marketing authorization holders [30]. This limitation may differentiate Japanese orphan drug designations from those in the US and the EU in the number of applications and applicant types.

Applications and annual reports for orphan drug designations were harmonized between the US and EU in 2007 and 2010, respectively [31-33], which may have helped reduce the time difference of designation between the US and the EU.

Within the regions for International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), these findings show that the US has the most first-in-ICH designations, the EU the second most and Japan the least. This finding is mainly attributable to the Japan-specific condition

requiring "high possibility of development" for orphan drug designations [23]. Only drugs with a high chance of approval may be designated as orphan drugs under Japanese guidelines.

In summary, these Japan-specific conditions of "orphan drug designations only with high possibility of development" and "the applicants for orphan drug designation to be future manufacturers" in Japanese regulations could be concluded as the root causes of time difference in Japanese approvals of orphan drugs. Easing these conditions and enabling the applicants to obtain the orphan drug designations are recommended. Early designation will be beneficial for the applicant not only in the regulatory and financial support but also beneficial to increase the visibility of the product. Once orphan designated, the designation will be public. It will increase the opportunity to conduct studies at multiple unfamiliar sites, to make the product visible from outside parties, and to obtain financial supports from them. These benefits should be emphasized.

3. Part 2

3.1 Background

Japanese academia has been pioneering cutting edge science such as gene therapy, induced pluripotent stem cells (iPS), innovative small molecules and biologics. Innovative drugs including orphan drugs which were originated by Japanese academia such as avermectin/ivermectin and nivolumab have been launched worldwide. Despite the inventions in Japan, the research and development of these drugs preceded in countries outside of Japan or no earlier than outside of Japan. For rare diseases, ivermectin was mainly developed in the US by Merck. It was approved for the treatment of strongyloidiasis in 2002 in Japan while it was approved in the US in 1996 [34-36]. Nivolumab was mainly developed in the US by Medarex and Bristol-Myers Squibb while their marketing approvals for melanoma coincided in 2014 both in Japan and the US [37,38].

While these inventions and innovations took place in Japan, as we described in the overview of Part 1, we have identified rooms for improvement/enhancement in agency-industry collaborations. The contribution of Japan for the worldwide patients in orphan drug development is limited in light of the numbers of orphan drug designations and marketing approvals compared with the US. In Part 2, we thus strived to focus on the academia-industry collaboration. The hypothesis was that there might be some room for improvement/enhancement in light of the numbers or nature of seeds for orphan drug development.

Some reviews of the collaboration gap between academia and industry in Japan have been conducted. One research reviewed a collaboration gap between venture companies and larger pharmaceutical companies in Japan. Commercially available or institutionally issued research papers were analyzed. In addition, a thorough interview was performed both to the venture companies and larger companies in Japan [39]. Another paper analyzed current status and potential solutions to overcome the "death valley" in drug development although the analysis did not focus on the orphan drugs non-quantitative/conceptual [40].

The seeds and technologies are the basis for the invention of novel therapies not only for ordinary non-orphan drugs but also orphan drugs. Historically, pharmaceutical industry had prioritized their own research and development. Such a research and development model faced a limited productivity along with the emerging progress in variety of science and technology. Western pharmaceutical companies have thus been eagerly pursuing various collaboration models instead of conventional collaboration model such as open crowdsourcing, academic centers of excellence, biotech co-creation, pharmaceutical peers risk sharing and innovation centers since as early as 2002 [41,42].

Japanese pharmaceutical companies followed these western pharmaceutical companies to pursue various collaborations with academia. Shionogi, Daiichi-Sankyo and Astellas initiated open innovation platform named FINDS, TaNeDS and a-cube in 2007, 2011 and 2011, respectively [43]. Under such a worldwide trend of increased academia-industry collaborations, there has been no quantitative analysis on the licensing and collaborative activities in Japan including their potential application for

orphan drugs.

We thus aimed to make a quantitative analysis on current status of academia-industry collaboration and the potential application for orphan drugs. We also aimed to identify the trend and point to focus in future academia-industry collaborations in Japan.

3.2 Method

Top 5 Japanese pharmaceutical companies were selected based on the SCRIP 100 total revenue ranking in 2013 [20]. Companies with pharmaceutical segment sales less than 50 % were removed from raking list. Takeda, Astellas, Daiichi-Sankyo, Eisai and Mitsubishi-Tanabe were thus selected. News releases from major Japanese pharmaceutical companies from January 2013 to March 2016 were used as source data. The nature and current status of the collaboration were identified. Our research focused on licensing and collaborative research in novel technology and new development candidates.

Type of collaborations were categorized with presence/absence of technological aspect, presence/absence of candidate product, type of licensor/collaborator, country of licensor/collaborator, and potential application for rare diseases. Technological aspect was categorized as present or absent. When the licensee can use specific technologies such as iPS technology, new manufacturing technology, IT/in-silico technology, it was judged as present. Presence/absence of candidate product was categorized as existing candidate, future candidate or unknown. Type of licensor/collaborator was categorized as academia, institution, industry and others. Country of licensor/collaborator was categorized as US, EU, Japan or others. Potential application for rare diseases was categorized as orphan drug designated, potential use anticipated, potential use unexpected or unknown. For example, when the target indication is oncology or metabolic diseases, it was judged as application potentially anticipated.

3.3 Result

Seventy licensing/collaborations were identified between 2013 and 2016 (Table 2). Annual number was almost stable between 20 and 22 from 2013 to 2015. Novel technology related to licensing/collaborations ranging from 40 to 59 % and accounted for 50% of all data (Figure 7(a)). Development candidate related to licensing/collaborations were dominant across years ranging from 82 to 95 % and accounted for 90 % of all data (Figure 7(b)). Licensing/collaborations for future development candidates accounted for as many as 39 % while those for existing candidates still accounted for 51 % of all data

The US was placed as a dominant country of partners accounting for 67 % of all data while the EU and Japan were 12 and 17 %, respectively (Figure 7(c)). The industry accounted for 70 % of all data as a type of partners, while academia, NPO and institution were 19, 10 and 1 %, respectively (Figure 7(d)).

New modalities such as gene therapy, cell therapy and nucleic acids accounted for 14 % of all data, 10 licensing/collaboration cases. Four, 5 and 1 of them were cell therapy, gene therapy and immuno-modulating nano-particle technology. The indications for cell therapy were Parkinson's disease, cardiac/metabolic/neurologic diseases, cancers and allergy. The indications for gene therapy were retinitis pigmentosa, Crohn's disease, and celiac disease/autoimmune diseases. The indication for nano-particle technology was celiac disease.

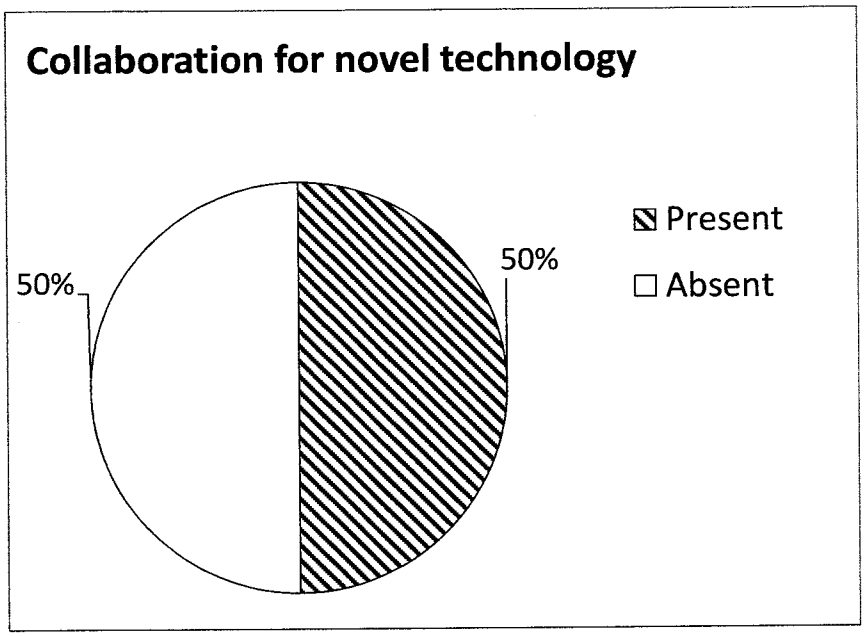
Potential use for rare diseases accounted for only 1 % of all data when orphan drug designation was used as an indicator, 1 licensing case for glatiramer acetate, a small molecule, whose indication is multiple sclerosis. When indications which may include rare diseases such as metabolic diseases and cancer were used as indicators, potential use for rare diseases accounted for 51 %, while such an analysis may be overestimating the potential use.

Table 2 Summary of licensing/collaboration in top 5 major pharmaceutical companies in Japan.

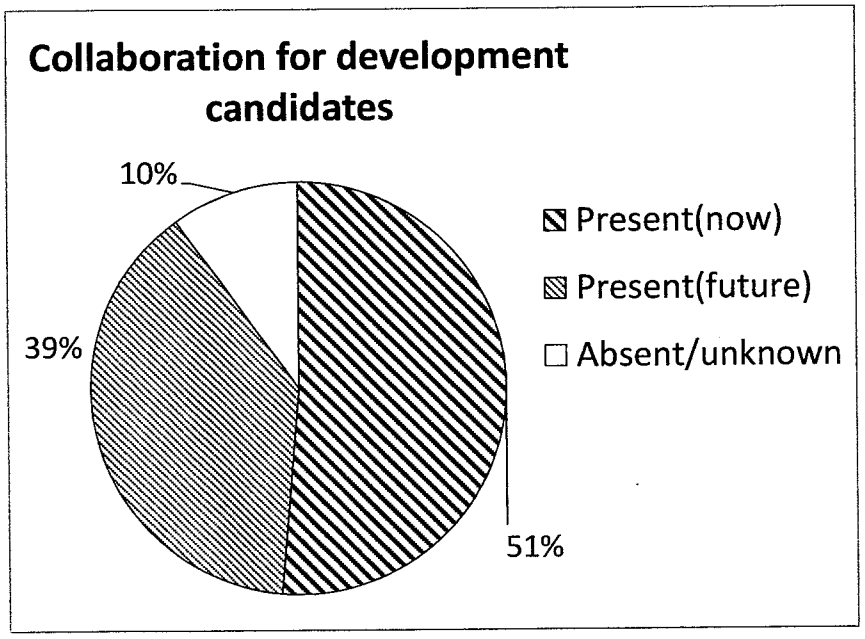
	2013	2014	2015	2016	Total
News release on licensing/collaboration					
Annual releases	20	21	22	7	70
Novel technology related					
Related	8 (40)*	9 (43)	13 (59)	5 (71)	35 (50)
Not related	12 (60)	12 (57)	9 (41)	2 (29)	35 (50)
Development candidates					
Candidate related	19 (95)	19 (91)	18 (82)	7 (100)	63 (90)
Licensing for existing candidates	10 (50)	10 (48)	12 (55)	4 (57)	36 (51)
Licensing for future candidates	9 (45)	9 (43)	6 (27)	3 (43)	27 (39)
Not candidate related or unknown	1 (5)	2 (10)	4 (18)	0 (0)	7 (10)
Country of partners					
US	13 (65)	18 (86)	11 (50)	5 (71)	47 (67)
EU	1 (5)	1 (5)	5 (23)	1 (14)	8 (12)
Japan	4 (20)	1 (5)	6 (27)	1 (14)	12 (17)
Others	2 (10)	1 (5)	0 (0)	0 (0)	7 (4)
Type of partners					
Industry	14 (70)	14 (67)	15 (68)	6 (86)	49 (70)
Academia	2 (19)	6 (29)	4 (18)	1 (14)	13 (19)
NPO	4 (20)	1 (5)	2 (9)	0 (0)	7 (10)
Institution	0 (0)	0 (0)	1 (5)	0 (0)	1 (1)
New modality (gene/cell therapy etc.)					
New modality	0 (0)	2 (10)	5 (23)	3 (43)	10 (14)
Conventional modality	19 (95)	13 (62)	12 (55)	4 (57)	48 (69)
Others	1 (5)	6 (29)	5 (23)	0 (0)	12 (17)
Potential use for rare diseases					
Designated as an orphan drug	1 (5)	0 (0)	0 (0)	0 (0)	1 (1)
Possible	11 (55)	8 (38)	12 (55)	5 (71)	36 (51)
Impossible or unknown	8 (40)	13 (62)	10 (45)	2 (29)	33 (47)

* Numbers in the parenthesis are the percentage for the annual releases

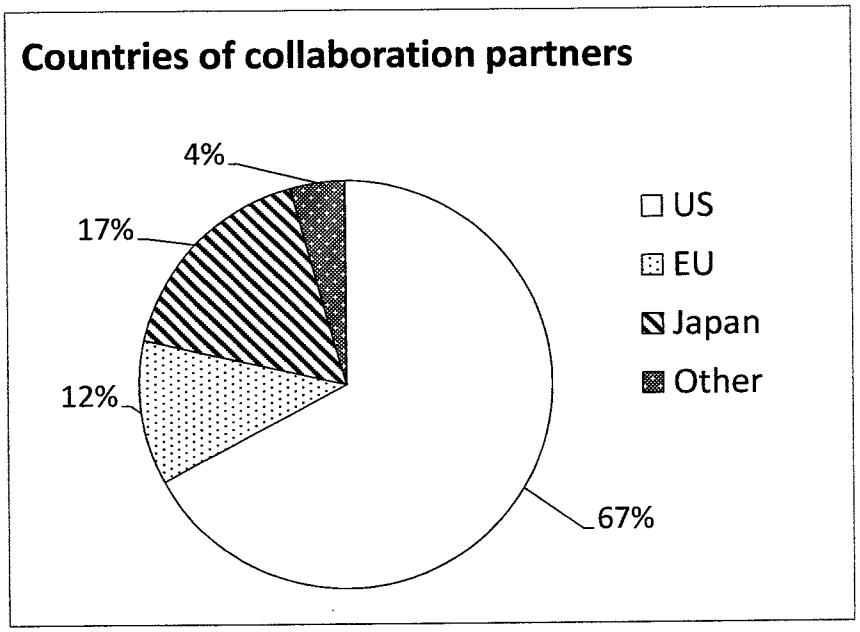
(a)


Collaboration for novel technology
50%
50%
Present
Absent

(b)


Collaboration for development candidates
10%
39%
51%
Present(now)
Present(future)
Absent/unknown

(c)



(d)

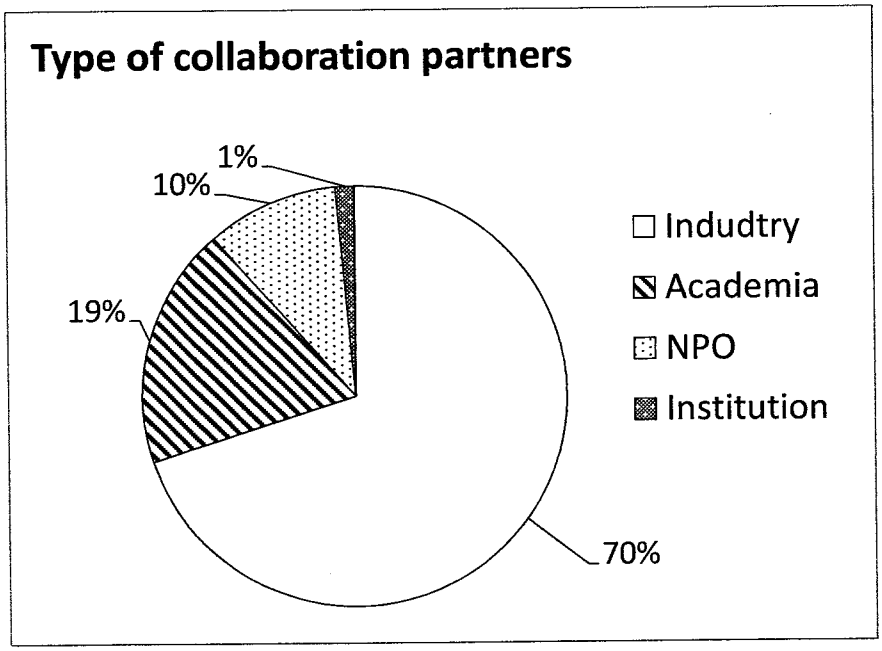


Figure 7 Analysis of the licensing/collaborations in Japanese top 5 pharmaceutical companies for collaboration for novel technology (Figure 7(a)), collaboration for development compounds (Figure 7(b)), country of collaboration partners (Figure 7(c)), and type of collaboration partners (Figure 7(d)).

Table 3 summarizes the cases of licensing/collaborations between Japanese academia and Japanese top 5 major pharmaceutical companies. Merely 6 out of 70 cases fell within this category. None of them were orphan drug designated. Among 6 cases, 3 were novel technology related, which were iPS, RNA-binding protein and in-silico technology. Two were new modalities, which were gene therapy and iPS and gene therapy.

Table 3 Summary of licensing/collaboration between Japanese academia and Japanese top 5 major pharmaceutical companies.

Company	Year	Licensing/ collaboration	Technological collaboration	Concrete candidate	Modality	Indications
Astellas	2016	Gene therapy in RPE	---	Existing	New	Retinal pigmentary dystrophy
Takeda	2015	iPS research for clinical application	iPS technology	Future	New	Cardiovascular, diabetes mellitus, neuro-diseases
Takeda	2015	Research for disease related RNA-binding protein	RNA-binding protein technology	---	---	Central nervous system, cancer
Takeda	2015	Collaboration with National Cancer Center	---	---	---	Oncology
Astellas	2013	In silico technology for anti-Dengue fever drug	in silico technology	Future	Conventional	Dengue fever
Astellas	2013	Collaborative research on the screening for anti-Dengue fever (NTD) with Nagasaki Univ	---	Future	Conventional	Dengue fever

RPE : Retinal Pigment Epithelium, NTD : Neglected Tropical Disease

3.4 Discussion

From the Japanese industry perspective, licensing and collaboration activities which are related to the future development of new drugs for rare diseases were limited. Only one case was identified as a designated orphan drug. It was a case of glatiramer acetate whose indication is multiple sclerosis. As of May 2016, the drug has been approved in Japan. However, its approval took place in Japan took place as late as September 2015 while that took place in the US in 1996. The time difference in marketing approvals was as large as 19 years [13,44].

There were 51 % of potentially applicable licensing/collaboration cases for rare diseases when the indications were used as indicators. This percentage may be considerably large one, however, and it should be interpreted with caution. All of the indication categories which may include rare diseases were counted as "potential use for rare disease" such as metabolic diseases and cancers. Fifty-one percent would be an overestimating percentage, and further studies will be warranted when indications of these cases will become clear at the timing of their marketing approvals. Taking above into consideration, it was hard to conclude that Japanese industry is intensively licensing or collaborating with their partners in rare disease areas. The acquisition of the research and development seeds for rare disease treatment coming from licensing/collaboration was limited. Further enhancement for the industry to acquire more seeds for rare disease treatment will be required.

From the Japanese academia perspective, there have been cutting edge researches

historically. There have been precedents which were originated by Japanese academia. Avermectin is a novel *streptomyces*-derived macrolide discovered by Prof. Ohmura in Japan. This discovery was followed by the development of ivermectin by collaborative work with Merck [34]. Ivermectin has proven its superb efficacy not only in veterinary area but also in clinical use in oncocerciasis. "HeartSheet" was invented by Prof Sawa, and assessed in a fashion of clinical research. Terumo has taken over its development. HeartSheet was approved in 2015 under new PMD Act [45]. iPS derived RPE cells for wet age-related macular degeneration (AMD) was developed by Prof. Takahashi's group of Riken in collaboration with Prof. Yamanaka of Kyoto University [46]. Early clinical assessment is currently being done by Riken in a fashion of clinical research. Helios and Dainippon-Sumitomo Pharma are to take over the following development and will be submitting the NDA in Japan [47].

Contrarily, in this research, merely 14 % of licensing/collaborations in regenerative medicine/novel modalities such as gene therapy and cell therapy were identified. A noteworthy finding was that there still have been 69 % of conventional modalities such as small molecules and biologics. These suggest that conventional modalities are still the key target area for research and development, and novel therapy is emerging steadily but slowly.

Compared with the advanced level of research in Japan, the ratio of regenerative medicine/new modality may be insufficient. In Japan, gene therapy have been intensively explored in the setting of clinical research (i.e., not in the setting of clinical trials for future new drug application). Cell therapy has been another research target,

and iPS was the first innovation in Japan proceeding to all other countries. These new modalities and/or technologies could serve as effective treatments for the diseases in which conventional treatments were not effective. Gene therapy is anticipated to be effective in hereditary metabolic diseases to compensate enzymatic deficiency. iPS is anticipated to be effective in rare diseases such as amyotrophic lateral sclerosis and spinal cord injury. Further enhancement for the academia and industry to closely collaborate each other for the realization of new therapy for untreatable diseases including rare diseases will be required.

The collaboration between Japanese academia and industry is thus considered as the key for success in Japanese orphan drugs. The circumstance in Japan is different from that in the US. Incubation of a novel research and development is limited in Japan while it is not in the US. Venture capitals to financially assist venture companies are limited in Japan while they are common in the US. This circumstance will not change instantly while the unmet needs for untreatable patients exist. Taking these into consideration, two-stage approach is recommended. For short term, both of academia and industry should enhance the utilization of existing mechanisms such as networks among academia/industry researchers and open innovation provided by the industry. Also, collaboration with recently established Japan Agency for Medical Research and Development (AMED) may be additional supplemental solution. AMED has just initiated a grant program for the companies which have candidates for orphan drugs during pre-orphan designation period [48]. For long term, improvement of incubational circumstance/environment for researches in academia and/or venture companies is required.

4. Overall Discussion

In Part 1, we found that the largest continued contribution to orphan drug development was from the US, followed by the EU and Japan. We note marked regional differences in the timing of designation, designation-approval ratios, applicant types, and drug types. A limitation of our study is that all of the drugs for rare diseases may not have been designated as orphan drugs due to the applicants' development strategy. Further studies are needed to validate the interpretation of our quantitative analysis on the orphan drug designations and their approvals.

Regulatory environments are changing rapidly and dramatically around the world. Novel mechanisms such as breakthrough designations, PRIME scheme and Sakigake have been implemented to hasten the development and approval of new drugs while their scope is not limited to orphan drugs but includes any drugs which meet their criteria. Despite these regional differences and shifting regulatory environments, annual numbers of orphan drug designations have been steadily increasing across all the examined regions since the legislation, with similar findings noted for innovative treatments with new modalities, such as cell and gene therapies.

Orphan drug legislation remains important as the only mechanism of drug development dependent upon patient population size along with the likelihood the product will have utility in the disease. Such legislation is considered crucial for ensuring the development of novel and efficacious medications targeting small and largely underserved segments of patients. Further research to explore a globally

optimized mechanism to aid orphan drug development including the harmonization of the designation scheme across ICH regions is warranted so that global orphan drug development can be enhanced in conjunction with other new priority programs. Our findings on regional differences could serve a basis for further exploration.

In Part 2, we found that orphan-drug designated licensing/collaboration case was only 1 out of 70 all licensing/collaboration cases. We also found that limited seeds or technologies have been provided from Japanese academia to Japanese major pharmaceutical companies. Most of the licensing/collaboration cases came from the US industry. Gene therapy and stem cell research have been explored for years in Japanese academia. Given such the most innovative and the most advanced researches have been made by Japanese academia, it is hard to illustrate that innovations and cutting edge science have been conveyed to the industry and patients in a timely fashion or in sufficient quantity. Further enhancement for academia-industry collaboration is required.

These analyses illustrate the current status and bottlenecks of orphan drug research and development from agency-industry and academia-industry perspectives in Japan. They also provide us with the basis to explore solutions for further enhancement of orphan drug development in Japan.

5. Conclusion

This novel research identified current status of the global and Japanese environment of orphan drug research and development. To enhance the research and development in Japan, particularly in seeds of Japanese origin, 2 measures are identified as potential solutions. One is to ease the regulations for orphan drug designations in Japan. The conditions of "orphan drug designations only with high possibility of development" and "the applicants for orphan drug designation to be future manufacturers" in Japanese regulations should be amended in the similar way to those of the US and EU. Another is to enhance/encourage academia-industry collaborations at earlier stage of research.

These will enable academia and industry to have broader opportunities to find the seeds/technology for orphan drugs, those to be guided/aided by the regulatory authority's consultations, and those to receive financial supports by the government or by the partners. By achieving these, novel medications will be conveyed to the patients with rare diseases earlier, and substantial part of currently existing huge unmet needs will be met.

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