Original Article

Analysis of Drug Lags and Designation Lags of Orphan Drugs Recently Approved in Japan

Fusako OURA¹,²* and Satoshi TOYOSHIMA²

Abstract

This study aims to understand the current situation and discuss elements that would further promote the development of orphan drugs in Japan. We analyzed drug lags (approval lags) and designation lags on orphan drugs approved as new drug categories in Japan over the past 5 years from 2010 to 2014. As a result, many of orphan drugs were developed in Japan after they were established in the US and the EU, and one-fourth at the maximum were developed locally for Japan. Regarding drugs that were first approved in the US or the EU ahead of Japan, Japanese median drug lags behind the US and the EU (lags of drugs that were considered spontaneously developed by pharmaceutical companies are in parentheses) were 50.0 (25.1) months and 34.8 (20.4) months, respectively. While Japanese drug lag issue for new medicines has recently been resolved, it was revealed that a longer drug lag behind overseas still exists in orphan drugs field. Japanese median designation lags behind the US and the EU were 63.8 (30.6) months and 46.7 (30.0) months, respectively. With further analysis and consideration, the drug lag and the designation lag in Japan are considered significantly attributable to a lag in development initiation or application for orphan designation. We consider it necessary to discuss revision of the existing designation criteria, development fee grant system operational procedures, and provision of incentives, aiming resolution of a lag in development initiation or application for orphan designation and further promotion of orphan drug development in Japan.

抄録

本研究では、日本での希少疾病用医薬品開発の現状把握とさらなる促進のための要素を考察することを目的とし、2010～2014年の5年间に日本で新薬薬品として承認された希少疾病用医薬品について、ドラッグラグ（承認ラグ）および指定ラグの調査・分析を行った。調査の結果、日本の希少疾病用医薬品開発はUS・EUの後追いタイプが多く、また日本ローカルのものが最大で1/4程度存在した。日本に先行しUSまたはEUで最初に承認された案件でのドラッグラグ（カッコ内は製薬企業が自発的に開発を行ったとみなすことのできる案件でのラグ）中央値はそれぞれUSから50.0（25.1）月、EUから34.8（20.4）月であった。一般的に日本での新薬薬品のドラッグラグ問題は解消されてきたという倾向の下にあっても、希少疾病用医薬品の世界においては依然として海外からのドラッグラグが大きいことが明らかとなった。指定ラグ中央値はそれぞれUSから63.8（30.6）月、EUから46.7（30.0）月であった。さらなる検討の結果、ドラッグラグおよび指定ラグの原因として開発着手でのラグ（開発着手ラグ）および指定申請でのラグ（指定申請ラグ）の影響が大きいことが考えられた。今後日本での希少疾病用医薬品の開発着手ラグおよび指定申請ラグの解消、さらなる開発促進に向けて、既存の指定基準や助成制度の

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（受付：2016.2.1 受理：2016.4.13）
Introduction

A rare disease is defined as a condition affecting a certain number or few people. There are thought to be more than 6,800 rare diseases in the United States (US)\textsuperscript{1)}, and there are numerous diseases with unknown etiology for which effective treatments have not been discovered yet. In general, predicting success in the research and development of medicines for rare diseases is challenging. It is because the limited number of patients causes difficulty in patient recruitment, and because diagnosis and efficacy indices may not have been established. In addition, there will most likely be few potential consumers of the new drugs even if the developed medicines are launched finally after an enormous effort, which may lead companies to make the judgment that there is a low possibility for investment recovery or low predictability for the market sales. Therefore, there are likely numerous cases that positive execution of research and development by the companies cannot be expected. To save patients who have no medicinal treatment option or who have not gained sufficient relief from currently available medicines, it is important to promote research and development on such rare diseases.

Some countries and regions including Japan have already developed specific legislations and policies to encourage the research and development of orphan drugs through some economic and regulatory incentives, which are to some extent similar but not the same\textsuperscript{2)}. Recently in Japan, in order to promote development of orphan drugs which will be used for in especially small number of local patients such as 1,000 or less in Japan, a guidance to evaluate efficacy and safety of such orphan drugs\textsuperscript{3)} is also established, supported by Health Labour Sciences Research Grant. The guidance provides points to be considered for reasonable evaluation on efficacy and safety with small number of subjects in clinical trials, stating that clinical development should be implemented flexibly and appropriately with consideration for each drug’s situation.

In the past, the drug lag issue not only for orphan drugs had been a major concern in Japan. The New Growth Strategy decided by the Japanese Cabinet in June 2010 declared “...we will work to resolve the drug lag and device lag as an urgent issue, improve the clinical trial environment, and expedite drug approval decisions\textsuperscript{4)}.” As a result of various attempts including a promotion to join global clinical trials, some recent reports show the drug lag issue is now in the process of being resolved. In terms of Japanese drug lag behind the US, a preliminary calculation resulted in 0.3 years in fiscal year 2012 and 1.1 years in fiscal year 2013, for new molecular entities (NMEs) including orphan drugs\textsuperscript{5)}. Another report showed the median lag for oncology drugs was 9.4 months in 2014 (as of July approval)\textsuperscript{6)}.

In this study, we focused on orphan drugs approved as new drug categories in Japan over the past 5 years from 2010 to 2014, to understand the current situation and discuss strategies for promoting further development, by
comparing the drug lag behind the US and the European Union (EU) and other related factors.

Methods

In this study, a "new drug" is defined as a drug with NME, new combination, new additional indication, new route of administration, new dosage, or a new dosage form. From all these new drugs approved in Japan from January 1, 2010 to December 31, 2014, we selected approvals of orphan drugs which are defined as drugs with orphan designations for examination in this study. This selection was based on the lists of approved new drugs disclosed on the Pharmaceuticals and Medical Devices Agency (PMDA) website and the list of Japanese orphan drugs on the National Institute of Biomedical Innovation (NIBIO) website. Influenza vaccines and anti-human immunodeficiency virus (HIV) or HIV-related medicines that are strongly influenced by local policies and prevalence of the disease or condition were excluded. In addition, we excluded those drugs that were approved with a review by PMDA but without a review by the First or Second Committee on New Drugs of Pharmaceutical Affairs and Food Sanitation Council under the Ministry of Health, Labour and Welfare (MHLW) because of their lighter application contents such as a slight change in indication or dosage and administration.

Based on the material available on the PMDA website, the following information was collected for the new orphan drugs as specified above. Marketing approval date was obtained from the lists of approved new drugs. Orphan designation date, new drug application (NDA) date for the marketing approval, application category, and approved indication were obtained from each review report. The orphan designation date was also obtained from the list of Japanese orphan drugs on the NIBIO website. The English words for the non-proprietary and brand names were cited from each Interview Form for the database search of the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) websites as stated later.

To study the situation in the US, the relevant information was collected from materials provided on the FDA website. We conducted a search of the Drugs@FDA database by using each non-proprietary name or brand name in Japan of the drugs for this study, to confirm the existence of marketing approvals which were comparable to that of Japan. Furthermore, the approval and NDA dates were obtained from each approval letter, review document, or both. In the same way, we conducted a search of the Orphan Drug Product Designation database, to confirm the existence of orphan designation and its date in the US. Similarly, we studied the situation in the EU by obtaining the same information in the EU based on the European Public Assessment Reports provided on the EMA website. The available information was limited to drugs that had been handled by the central authorisation procedure. The existence of orphan designation and its date in the EU were also referred to on the Rare disease (orphan) designations database. Where necessary, brand names in the US and the EU were used for a supplementary search in the EMA and FDA databases respectively. When no matched drugs were found on the FDA and EMA databases with the English words of the non-proprietary or brand name of each drug, the drug was handled as one that has not existed in the US or
the EU. This means drugs where the entities were registered only with chemical names in the database were not counted.

1. Comparison among the three regions for the status of orphan designation and marketing approval

A comparison of the orphan drugs was conducted on the status of orphan designations and marketing approvals in the US and in the EU of those comparable to Japan, focusing on the same products in the three regions. The comparison was not made for different products as generic drugs even when the FDA and the EMA databases showed the same non-proprietary names to those of Japan. The comparison was made as long as they included common disease names with those of Japan, even when the indication wordings in the US or in the EU were different from Japan. Specifically, we compared the earliest date of an orphan designation or marketing approval in the US or in the EU having common disease names with Japan, if any difference exists for target patient population or difference exists by a simultaneous approval for multiple indications in any of the three regions. When the orphan designations or marketing approvals had been withdrawn for reasons such as the period of market exclusivity expired in the US or the EU, the original information provided before the withdraw were used to compare the three regions. The cutoff date for this study was October 21, 2015, and any information after this date is not included in the analysis. The original designation date in Japan was adopted when the orphan designation date is changed or added by the development sponsorship transfer or addition, or redesignation to expand the designation range during the NDA review period.

2. Drug lag and designation lag

In this study, “drug lag” is defined as marketing approval lag, and “designation lag” is defined as orphan designation lag. These lags were calculated first on a daily basis and later converted into months by comparing the Japanese marketing approval date or orphan designation date against those of the US and the EU. For these calculations, 1 month was deemed as 30 days and rounded to one decimal place.

3. Stratified analyses on drug lag and designation lag

By the Japanese review report and NDA document, we confirmed whether or not each drug had been evaluated by the governmental working committees, including the Evaluation Committee on Unapproved Drug Usage Matter, the Evaluation Committee on Pediatric Medicinal Treatment, and the Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs. Additional stratified analyses on the drug lag and the designation lag were conducted based on whether the drugs were evaluated by the above-mentioned Committees or whether those were NMEs.

4. Comparison of milestone period to marketing approval

The period from NDA to marketing approval and the period from orphan designation to NDA took in the three regions were calculated and compared based on the dates of orphan designation, NDA, and marketing approval. The same calculation method as the drug lag was used.

Results

A total of 635 new drugs including 85 orphan drugs obtained marketing approvals in Japan
from 2010 to 2014. Following the exclusion as specified previously, 68 new orphan drugs remained for investigation in this study. There was one case of public knowledge-based application or “Kouchi Application”, in which NDA can be submitted based on common knowledge and facts on off-label use or much use experiences abroad without conducting clinical trials overall or partially in Japan.

1. Comparison among the three regions for the status of orphan designation and marketing approval

For the total 68 orphan drugs, Fig. 1A compares the percentage of the first designation or the first marketing approval among the three regions. Most of the orphan designations or marketing approvals were obtained first in the US prior to Japan or the EU. Although 24 drugs (35%) have obtained the orphan designations and 20 drugs (29%) have obtained the marketing approvals first in Japan, most of them, 18 of the 24 drugs (26% of the 68 drugs) and 16 of the 20 drugs (24% of the 68 drugs), are designated and approved only in Japan as of the cutoff date of the study, respectively. The requirement of the local patient number for orphan designation varies across the three regions: for the US, less than 200,000; for the EU, 5 or less per 10,000 people; and for Japan, less than 50,000, with a few exceptions. Therefore, it should be noted that the same product may obtain orphan
The drugs designated or approved only in Japan as of the cutoff date of the study cannot be judged as of now whether to be developed in the US or the EU in the future or to remain as Japanese local developments. Therefore, as for the rest, only 6 orphan designations and 4 marketing approvals should be deemed as drugs for which Japan is ahead of the US and the EU in obtaining orphan designation or marketing approval. Analysis of the designated and approved drugs among all three regions (Fig. 1B) showed that most were designated or approved first in the US, while only 1 drug (5%) was designated first in Japan.

All new orphan drugs for this study were divided into three categories: “ex-JPN prior approval” that were first approved in the US or the EU ahead of Japan; “JPN prior approval” that were first approved in Japan ahead of the US or the EU; and “only JPN approval” that were approved only in Japan as of the cutoff date of the study. The 68 new orphan drugs were composed of 48 “ex-JPN prior approvals”, 4 “JPN prior approvals”, and 16 “only JPN approvals”. The “only JPN approval” includes 9 cases, the drugs from domestic human plasma fractions which are not for export, and the drugs with active ingredients that had already been used ex-Japan. Excluding aforesaid 9 cases, the number of “only JPN approval” will be 7 only. The number of “only JPN approval” and “JPN prior approval” is much smaller than that of “ex-JPN prior approval”.

The above implies that, among the three regions, the US is the most advanced in the timings of orphan designation and marketing approval for orphan drugs. In addition, many of orphan drugs were developed in Japan after they were established in the US and the EU, and one-fourth at the maximum were developed locally for Japan.

2. Drug lag

Drug lags of the “ex-JPN prior approvals” are shown in Table 1. Regardless of the EU approval order, Japanese median drug lag behind the US was 50.0 months with a mean of 80.9 months for the 43 orphan drugs approved in Japan behind the US. Although the methods were different from those of our study, another research similarly reported a significant approval lag in Japan behind the US, which averaged 54 months, for orphan drugs designated as of 20123). Furthermore, regardless of the US approval order, Japanese median drug lag behind the EU was 34.8 months for the 35 orphan drugs approved in JPN behind the EU. Based on the number of first designations and marketing approvals as mentioned previously as well as the drug lags, the US was significantly ahead of Japan in the development of orphan drugs. As a reference, the drug lags of the “JPN prior approval” which indicates how long Japan was ahead of the US and the EU, resulted in a median of –10.9 months from the US for 3 drugs and –13.0

<table>
<thead>
<tr>
<th>Lag behind US (month)</th>
<th>Lag behind EU (month)</th>
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<tr>
<td>N</td>
<td>mean</td>
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<tr>
<td>43</td>
<td>80.9</td>
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Table 1 Drug lag of the “ex-JPN prior approvals”
months from the EU for 2 drugs.

3. Stratified analyses on drug lag

The Committees as specified in the Methods section has been established by MHLW with a view to addressing the issue of unapproved drugs or off-label uses of drugs in Japan. Following the results of the Committees, MHLW has encouraged, requested, or invited pharmaceutical companies for early development or NDA on the new drugs including new additional indications. Those drugs that had not evaluated by the Committees can be regarded as having been developed spontaneously by pharmaceutical companies. In order to interpret more deeply on the current situation of the development of orphan drugs in Japan, we thought it necessary to perform stratified analyses based on whether the drugs were evaluated by the Committees. Moreover, considering the potential impact of the NME status on the development speed, additional stratified analyses were conducted depending whether the drugs were NMEs or not.

Out of the 68 orphan drugs, 36 had not while 32 had been evaluated by the Committees. As shown in Table 2, the “ex-JPN prior approvals” not evaluated by the Committees demonstrated drug lags behind the US and the EU with medians of 25.1 and 20.4 months for 19 and 16 drugs, respectively. The “ex-JPN prior approvals” evaluated by the Committees demonstrated three to four-fold longer drug lags compared to those not evaluated by the Committees. Without the Committees’ intervention, these orphan drugs would not have been approved or even achieved any stages of development, or would have been approved with much longer drug lags.

Out of the 68 orphan drugs, 45 were NMEs while 23 were not, and the non-NMEs consisted of 22 drugs with a new additional indication and 1 drug with a new route of administration. As a reference, the NME status was not imbalanced by whether they were evaluated by the Committees or not.

Out of PMDA’s preliminary calculation\textsuperscript{5}), regardless of whether the entities were orphan drugs, Japanese drug lag for the NMEs behind the US (lags of drugs excluding those that proceeded to NDA following the result of Evaluation Committee on Unapproved or Off-labeled

<table>
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<th>Table 2</th>
<th>Drug lag of the “ex-JPN prior approvals” analyzed for whether to be evaluated by Committees</th>
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<td>Lag behind US (month)</td>
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<td>N</td>
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<tr>
<td>All</td>
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<tr>
<td>Evaluated by Committees</td>
<td>24</td>
</tr>
<tr>
<td>Not evaluated by Committees</td>
<td>19</td>
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Drugs with High Medical Needs are in parentheses) was 1.7 years (1.4 years) in FY*¹ 2010, 1.6 years (0.5 years) in FY 2011, 0.3 years (0 year) in FY 2012, and 1.1 years (0.4 years) in FY 2013. Regarding the orphan drugs approved in Japan from January 1, 2010 to December 31, 2014, Japanese median drug lag for the NMEs behind the US (lags of drugs not evaluated by the Committees are in parentheses) was 48.6 months or 4.1 years (25.1 months or 2.1 years) as shown in Table 3. To compare our analysis with the PMDA’s report, we calculated the median drug lag by approval fiscal year as shown in Fig. 2. Japanese median drug lags for the all NMEs with orphan designation in this study was 3.1 years for 7 drugs in FY 2010, 3.6 years for 6 drugs in FY 2011, 4.4 years for 7 drugs in FY 2012, 6.0 years for 4 drugs in FY 2013, and 4.4 years for 9 drugs in the period from April to December 2014. It shows the drug lags on NMEs of orphan drugs had been extending until FY 2013 and were longer than those reported on NMEs by PMDA. In addition, an additional stratified analysis was conducted for the orphan drugs not evaluated by the Committees, that is, for the orphan drugs developed spontaneously by pharmaceutical companies. Despite the limited number of the drugs per FY, it resulted in 2.5 years for 5 drugs in FY 2010, 1.0 years for 3 drugs in FY 2011, 0.4 years for 1

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<th>Lag behind US (month)</th>
<th>Lag behind EU (month)</th>
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<td></td>
<td>N mean median min max</td>
<td>N mean median min max</td>
</tr>
<tr>
<td>All</td>
<td>43 80.9 50.0 3.4 394.3</td>
<td>35 52.8 34.8 0.9 207.3</td>
</tr>
<tr>
<td>NME</td>
<td>33 87.4 48.6 3.4 394.3</td>
<td>29 53.5 34.8 1.9 207.3</td>
</tr>
<tr>
<td>Not NME</td>
<td>10 59.3 53.3 7.0 176.6</td>
<td>6 49.7 42.2 0.9 113.6</td>
</tr>
<tr>
<td>NME not evaluated by Committees</td>
<td>15 30.0 25.1 3.4 96.7</td>
<td>13 20.0 22.5 1.9 46.9</td>
</tr>
</tbody>
</table>

Fig. 2  Drug lag behind the US of “ex-JPN prior approval” analyzed for NME per approval fiscal year
drug in FY 2012, 0.3 years for 1 drug in FY 2013, and 2.7 years for 5 drugs in the period from April to December 2014. For NMEs of orphan drugs which were developed spontaneously by pharmaceutical companies, the drug lags had been decreasing until FY 2013, and they stepped close to those on NMEs excluding those evaluated by Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs reported by PMDA. While a drug lag issue for new medicines in Japan has recently been resolved, it was revealed that a longer drug lag behind overseas still exists in orphan drugs field. However, this drug lag in orphan drugs reflects the achievements of the Committees to make medicines which had been available in other major countries but not in Japan for a long time, accessible to Japanese patients.

4. Designation lag and a stratified analysis

For orphan drugs, measures are taken in all three regions to support the research and development activities by pharmaceutical companies. With local variation, those incentives commonly include a development fee grant system, lower user fee for NDA, and longer period of market exclusivity\(^2\) which pharmaceutical companies can utilize from the developmental stage to the post-marketing stage.

Designation lags and stratified analyses are shown in Table 4, for 44 approved drugs which were designated first in the US or the EU as indicated in Fig. 1A. Regardless of the EU designation order among the three regions, Japanese median designation lag behind the US was 63.8 months with a mean of 89.2 months for 42 approved drugs which were designated in Japan behind the US. Although the methods were different from those of our study, another research similarly reported a significant designation lag in Japan behind the US, which averaged 53 months, for orphan drugs designated as of 2012\(^3\). In addition, regardless of the US designation order among the three regions, Japanese median designation lag behind the EU was 46.7 months for the 26 approved drugs which were designated in Japan behind the US. Although the methods were different from those of our study, another research similarly reported a significant designation lag in Japan behind the US, which averaged 53 months, for orphan drugs designated as of 2012\(^3\). In addition, regardless of the US designation order among the three regions, Japanese median designation lag behind the EU was 46.7 months for the 26 approved drugs which were designated in Japan behind the US. The general designation lags behind the US and the EU were longer than the drug lags of the “ex-JPN prior approvals”. The result of a stratified analysis demonstrated Japanese median designation lags behind the US and the EU were 30.6 months for 19 approved drugs and 30.0 months for 12 approved drugs that had not been evaluated by

<table>
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<th>Table 4</th>
<th>Designation lag of drugs that were designated first in the US and in the EU</th>
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<tr>
<td></td>
<td>Lag behind US (month)</td>
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<tr>
<td></td>
<td>N</td>
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<tr>
<td>All</td>
<td>42</td>
</tr>
<tr>
<td>Evaluated by Committees</td>
<td>23</td>
</tr>
<tr>
<td>Not evaluated by Committees</td>
<td>19</td>
</tr>
<tr>
<td>NME</td>
<td>33</td>
</tr>
<tr>
<td>Not NME</td>
<td>9</td>
</tr>
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</table>
the Committees, respectively. Similar to the stratified analysis result for the drug lag of the “ex-JPN prior approvals” in Table 2, the orphan drugs evaluated by the Committees demonstrated approximately three-fold longer designation lags than those not evaluated by the Committees. The designation lag of the NMEs was longer than that of the non-NMEs was in both the mean and median.

Additionally (data not shown), Japanese designation lag was calculated for the “ex-JPN prior approvals” for which designation dates were available regardless of the designation order among the three regions. As a result, Japanese median designation lags behind the US and the EU were 58.1 months for the 38 approved drugs and 41.3 months for the 25 approved drugs, respectively, which were longer than the Japanese drug lag of the “ex-JPN prior approvals”. In addition, an individual comparison between designation lag and drug lag for these “ex-JPN prior approvals” shows that about 70% (compared with the US and the EU, 26/38 and 17/25 drugs, respectively) demonstrated longer lags in designation than in the marketing approval (drug lag).

### 5. Comparison of milestone period to marketing approval

The period from NDA to marketing approval, or NDA review period (Table 5), and the period from orphan designation to NDA (Table 6) were compared for 19 drugs that had all of orphan designation, NDA, and marketing approval dates in all three regions. The result in Table 5 revealed that Japanese NDA review period is not inferior to those of the US and the EU in any way, while the median of the NDA review period in the US was the shortest. The one case of public knowledge-based application was not included for this comparison.

All three regions requested applications for orphan designation prior to submitting NDAs. In addition, in Japan, orphan designation may not be allowed for those drugs that are considered to have completed the developmental process in Japan at the time of the application for orphan designation\(^{18}\). Table 6 shows a median period from orphan designation to NDA in Japan was 10 months shorter than those for the US and the EU. The findings from Table 6 was considered attributable to the longer lags in designation than in marketing approval, suggesting the timing of obtaining orphan designation in the course of development in Japan may be at a later time.

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**Table 5** Comparison of the period from NDA to marketing approval (N=19)

<table>
<thead>
<tr>
<th>NDA to marketing approval (month)</th>
<th>JPN</th>
<th>US</th>
<th>EU</th>
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<tbody>
<tr>
<td>mean</td>
<td>9.8</td>
<td>9.0</td>
<td>14.7</td>
</tr>
<tr>
<td>median</td>
<td>9.2</td>
<td>6.1</td>
<td>14.6</td>
</tr>
<tr>
<td>min</td>
<td>6.9</td>
<td>4.8</td>
<td>8.9</td>
</tr>
<tr>
<td>max</td>
<td>13.6</td>
<td>36.4</td>
<td>22.4</td>
</tr>
</tbody>
</table>

**Table 6** Comparison of the period from orphan designation to NDA (N=19)

<table>
<thead>
<tr>
<th>Orphan designation to NDA (month)</th>
<th>JPN</th>
<th>US</th>
<th>EU</th>
</tr>
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<tbody>
<tr>
<td>mean</td>
<td>15.7</td>
<td>23.6</td>
<td>27.8</td>
</tr>
<tr>
<td>median</td>
<td>14.9</td>
<td>25.1</td>
<td>27.0</td>
</tr>
<tr>
<td>min</td>
<td>0.6</td>
<td>–7.4</td>
<td>–7.4</td>
</tr>
<tr>
<td>max</td>
<td>44.2</td>
<td>55.7</td>
<td>96.7</td>
</tr>
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Note: The period of orphan designation after NDA is expressed in minus.
point compared to the US and the EU.

Furthermore, we confirmed the approval status in the US and in the EU when they obtained orphan designation in Japan for “ex-JPN prior approvals” which have not evaluated by Committees. As a result, out of 19 drugs approved behind the US without being evaluated by Committees, 9 drugs had been already approved in the US when they were designated in Japan. Out of 16 drugs approved behind the EU without being evaluated by Committees, 7 drugs had been already approved in the EU when they were designated in Japan. Even for those which were developed spontaneously by pharmaceutical companies, about a half resulted in obtaining the orphan designation in Japan after marketing approvals in the US or the EU.

For reference, in Japan, applicants are recommended to consider that it may take several months for reviewing the application for orphan designation\textsuperscript{18}, however, Japanese review period for orphan designation is unlikely to take much longer than those in the US and the EU.

Considering the above, the drug lag and the designation lag in Japan are considered significantly attributable to a lag in development initiation or applications for orphan designations by pharmaceutical companies.

**Discussion**

The orphan designations as of June 2012 totaled to 269 in Japan, much less compared to 2,609 in the US and 1,000 in the EU\textsuperscript{2}. The difference in the implementation year of the legislations and policies on orphan drugs should be carefully interpreted: the US started the framework in 1983, Japan in 1993 while the EU started in the year 2000. The differences of the requirement for orphan designation regarding the number of local patients in the three regions are as previously described. When the intended use is for a particular intractable disease which lacks established treatment options, the requirement of number of patients in Japan was expanded on April 1 2015, to allow more than 50,000 patients, if it falls to approximately one-thousandth of entire Japanese population\textsuperscript{17, 19}. In addition, Japanese designation criteria include “a particularly superior usage value”\textsuperscript{16} which means high “medical needs” (the drugs or medical devices should be indicated for the treatment of serious diseases, satisfying either of the following criteria: 1) there is no appropriate alternative drug/medical device or treatment, 2) the product is expected to have a significantly higher degree of efficacy or safety than existing products)\textsuperscript{18–20}. Furthermore, Japanese designation also requires “possibility of development”\textsuperscript{19} (applicants should explain it based on existing non-clinical and clinical data in the latter half of the phase I study or in the first half of the phase II study except when the product has already been approved overseas or sufficient clinical study data are available)\textsuperscript{18, 20}. The EU also includes the medical needs requirement “…there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition”\textsuperscript{15} and “significant benefit” means a clinically relevant advantage or a major contribution to patient care\textsuperscript{21}. The requirement for possibility of development is unique to Japan\textsuperscript{2}. With the current Japanese criteria, drugs with higher possibility and foreseeable success in their development are more easily designated, on the other hand, those drugs that have uncertainty in
marketing approvals yet have hurdles to be designated. Table 4 indicates that Japanese designation lags behind the US and the EU tends to be shorter in non-NMEs than in NMEs, although the small number of non-NMEs should be carefully interpreted. We consider that non-NMEs are more easily designated, because more data for them had been accumulated at the initial approvals. Table 6 suggests the timing of obtaining orphan designation in the course of development in Japan may be at a later time point compared to the US and the EU. This also indicates a situation where the Japanese orphan designation criteria restricts the timing available for obtaining the orphan designation.

Moreover, Japanese development fee grant system, which is one of the incentives for orphan designation, possibly restricts the application timing and the number obtaining orphan designation in Japan. It may be considered that, in order to effectively allot the limited grant budget, Japan designates those drugs with higher possibility and foreseeable success, and prevents those drugs with yet uncertainty to gain marketing approvals, from obtaining their rights to apply for a grant. Considering the above, current Japanese designation criteria and development fee grant system may lead to the limited number and timings of application/obtainment of orphan designation.

From the results of this study, a large drug lag behind overseas still exists in the orphan drugs field. Spontaneous development on orphan drugs by pharmaceutical companies is expected to proceed furthermore, leading to shortening the drug lag in Japan. The drug lag and the designation lag in Japan are considered significantly attributable to a lag in development initiation or applications for orphan designations by pharmaceutical companies. These results suggest that it would require discussing to revise existing designation criteria, development fee grant system operational procedures, and provision of incentives, aiming resolution of a lag in development initiation or applications for orphan designations and further promotion of orphan drug development in Japan.

To increase the number and to allow for earlier designation in Japan would enable a pharmaceutical company to better utilize and predict Japanese incentives of the orphan designation, such as preferential advice, priority review, and 10 years re-examination period. Moreover, the potential advantage of premium at the National Health Insurance price listing or price revision would raise company's expectation for investment recovery and payability on the developmental drugs. This should motivate pharmaceutical companies to go in for early development and positive investments, resulting in shorter lag in development initiation. On top of that, aiming to shorter lag in application for the orphan designation, we consider there should be room to revise the grant system. For instance, it can be that designation and granting system are independent of each other, that the applicant can easily obtain earlier orphan designations when the applicant does not request for the granting system, and that the drug's possibility to obtain a marketing approval is discussed when selecting the candidates to be granted. In addition, as an option, the operational procedures of the grant system should permit pharmaceutical companies to receive the grants even after three years until the accumulated amount reaches to the pre-specified total limit for each drug. That revision would allow pharmaceutical companies to utilize the grants more flexibly. Moreover,
orphan drug development in Japan can be further promoted by installing new incentives that help pharmaceutical companies to better foresee investment recovery and payability on the developmental drugs, and that can also be applied to other developmental drugs as like a priority review vouchers in the US\textsuperscript{22} whose entitlements may be transferred, including by sales, to another company or could be used for another product.

**Conclusion**

While a drug lag issue for new medicines in Japan has recently been resolved in general, it was revealed that a longer drug lag behind overseas still exists in orphan drugs field. It is considered some orphan drugs have been developed specifically only for Japan. However, many of orphan drugs were developed in Japan after they were established in the US and the EU, whereas few drugs were first designated or approved in Japan ahead of the US and the EU. The drug lag and the designation lag in Japan are considered significantly attributable to a lag in development initiation or applications for orphan designations. We consider it necessary to discuss revision of the existing designation criteria, development fee grant system operational procedures, and provision of incentives, aiming resolution of a lag in development initiation or applications for orphan designations and further promotion of orphan drug development in Japan.

**References**


14) Code of Federal Regulations Title 21, PART 316: ORPHAN DRUGS.


Notes

*1 fiscal year (FY) means from April to March in Japan.