Effective Use of Foreign Clinical Data in Approvals for Medical Devices in Japan

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Abstract

Initial clinical development of medical devices occurs mainly in the USA and EU, with many medical devices registered in Japan afterwards. As the clinical performance of medical devices is less sensitive to ethnicity than the efficacy and safety of a drug, the performance of such devices can often be evaluated using foreign clinical data. The factors affecting the requirement for Japanese clinical data was investigated in the Japanese approvals of 103 high-risk devices, occurring between April 2005 and March 2015. The requirement for Japanese clinical data was associated with no approval in the USA and EU and the absence of foreign clinical data in the submission ($p<0.001$). Our results suggest that Japanese clinical data are not an essential requirement when foreign clinical data are included in the Japanese data package for approval, although, for 50% of devices with approval in the USA or EU, Japanese clinical data were still required for the Japanese approval. Reasons for this included the possibility that the performance of the device was sensitive to ethnicity associated with the medical environment, and that the device had been updated from the original one.

Keywords: regulatory science, medical devices, medical device development

1. Introduction

The development of medical devices faces different regulatory frameworks in the United States of America (USA), the European Union (EU), and Japan. For the protection of public health, the regulation of a medical device usually requires it to be classified according to the risk it poses to consumers [1]. Therefore, each regulatory agency determines the approval process and the data package required according to the risk classification of the particular device. For example, medical devices in the USA are categorized into three classes (Class I, II, and III). Although Class I (low risk) devices are exempt from premarket notification, Class II (moderate risk) devices are required to be accompanied by clinical data, as necessary for the premarket notification (510k) review process, and Class III (high risk) devices require clinical data for the premarket approval (PMA) review process by the Food and Drug Administration (FDA) [2, 3, 4]. In the EU, medical devices are categorized into four classes (Class Ia, IIa, IIb, and III), and clinical data are essential for Class III devices [2, 3, 4]. In Japan, the category consists of four classes (Class I, II, III, and IV). Class I (low

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ducing and/or removing such delays [6]. As a result, the assessment time has been shortened from 16 to 9.5 months [7], and the assessment lag of around 0.5 years has been removed [8].

In contrast to the situation with drugs, the performance of medical devices is insensitive to ethnicity, and in many cases the extrapolation of foreign clinical data to a new region has been acceptable for regulatory review. However, a development lag for medical devices still remains in Japan. One reason for this may be that Japan has a smaller market size than the USA and EU. Efficient device development requires the initial focus to be on a larger market; the data package is therefore first prepared for the USA/EU registration. As discussed above, there are differences in the device categories and regulatory requirements across the three regions. Even though complete data packages may exist for the USA/EU, different or additional data packages may be required for Japanese registration. Moreover, if additional data from a clinical study are required, there will be a substantial time lag associated with completion of the clinical study, and additional regional development costs will be incurred.

The purpose of this study was therefore to investigate any correlation between the requirement for a Japanese clinical study, and the timing of approval in the USA/EU. In Japan, a clinical study is an essential requirement for new devices (Class III or IV), even if no clinical study was carried out for registration in the USA/EU.

2. Materials and Methods

2.1. Data Sources

All information used in this study was extracted from review reports for new devices in Class III or Class IV; these were published on the website of Japan’s PMDA [9]. For this study, the approval status in the USA or EU at the time the device was submitted for approval in Japan was investigated and categorized as either “No approval in the USA and EU” or “Approval in the USA or EU”. The status “Approval in the USA or EU” was also given if the device was under review in the USA or EU.

For the approval status, the information on approval date in the USA or EU was obtained from the PMDA [9] and FDA websites [10]. A medical device with more than one brand name (i.e., with each brand name sold via a different channel) was counted as a single device.

Medical devices approved using safety and/or efficacy evidence that referred only to previous reports, and devices approved without any clinical information, were excluded from this study.

2.2. Data Analyses

Fisher’s exact test was used to examine factors affecting the requirement for Japanese clinical data in the approval of high-risk devices in Japan. The variables were the approval status in the USA or EU (no approval or approval), whether foreign clinical data were used, the classification of the device (Class IV or not), and the status of orphan/priority review/expedited review devices.

Statistical analyses were conducted using SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC).

3. Results

One hundred and three high-risk devices were approved in Japan between April 2005 and March 2015 (Supplemental Figure A.1). Regarding the origin of clinical data, 45 devices (44%) were approved using only foreign clinical data, 22 devices (21%) were approved using both foreign and Japanese clinical data, and 36 devices (35%) were approved using only Japanese clinical data. Japanese clinical data were used for 56% (21% plus 35%) of devices. As the performance of a medical device is insensitive to ethnicity, it was assumed that foreign clinical data were used without additional Japanese clinical data when medical devices had been registered following approval in.
other countries. However, the results showed this assumption to be incorrect.

We then investigated the status of approval in the USA and EU, to examine whether this status affected the requirement for Japanese clinical data in the Japanese approval. The number of cases with or without prior approval were 89 (86%) and 14 (14%), respectively. These results revealed that 86% of devices were registered after approval in the USA or EU, suggesting the possibility that foreign clinical data were used for the Japanese submission. However, 50% of devices with approval in the USA or EU were submitted for approval in Japan with Japanese clinical data (Figure 2). It is supposed that the foreign clinical data were considered insufficient to indicate efficacy and safety in Japanese patients. For 25% (22 devices) of devices with approval in the USA or EU, Japanese clinical data were used without the foreign clinical data (Figure 2). However, all those devices with no approval in the USA and EU (14 devices) required Japanese clinical data (Figure 2).

We also investigated the trend in the number of approvals by year. Although the number of approvals changed each year, the percentage with no prior approval in the USA or EU was between 0% and 20% (Figure 3) and had no specific trend. Therefore, it was concluded that analyses by year were not necessary.

Of the total 103 device approvals, the numbers of priority review devices, expedited review devices, and orphan devices, were 18 (17%), 1 (1%), and 8 (8%), respectively (Supplementary Figure A.1). As priority review or orphan applications were made for devices used for serious diseases[11, 12, 13, 14], it
was supposed that there were difficulties with conducting a clinical trial in Japan. However, five devices (19%) had no approval in the USA and EU. Of the 22 devices (81%) with approval in the USA or EU, 15 (68%) required foreign and Japanese data, and one (5%) was submitted with only Japanese data. Thus, Japanese data were used for 32% of these priority review or orphan devices.

Fisher’s exact test was used to identify factors affecting the requirement for Japanese clinical data for approvals in Japan (Figure 4), and demonstrated that a requirement for Japanese clinical data was associated with no approval in the USA and EU, and the absence of foreign clinical data ($p < 0.001$). No significant associations were found for Class IV designations ($p = 0.552$) and the status of orphan/priority review/expedited review devices ($p = 0.178$).

In cases with approval in the USA or EU, for which a data set sufficient for the USA or EU registration was available, additional Japanese data were submitted alongside the foreign clinical data in 25% (22 devices) of cases, while only Japanese clinical data were used for another 25% (22 devices) of cases (Figure 2). We therefore examined the reviews to investigate why Japanese clinical studies were required (Supplemental Figure A.1).

First, if the approval category were 510k in the USA, or CE mark in EU, the submitted package would not include clinical data. Therefore, for 22 devices submitted with only Japanese clinical data in 25% (22 devices) of cases, while only Japanese clinical data were used for another 25% (22 devices) of cases (Figure 2). We therefore examined the reviews to investigate why Japanese clinical studies were required (Supplemental Figure A.1).

As a result, the approval categories were PMA and CE mark (5 devices), PMA only (1), 510k and CE mark (10), CE mark only (6).

In the USA, when a device performance is similar to a previously approved device, the device is approved without the clinical data in 510k process [2, 3, 4]. Therefore, the device which has been improved and approved repeatedly in 510k process, has no clinical data. Similarly, for CE mark in EU, since clinical data are not mandatory for devices of Class III [2, 3, 4], no clinical data often exist for the devices. In these cases, Japanese clinical data are required for Japanese first submission (Figure 5).

For PMA process in the USA, clinical data are essentially required [2, 3, 4]. However, there are some exceptions. In our investigation, two devices (no.40,41) of six devices with PMA were approved without clinical data in the USA, which required Japanese clinical data.

Although even in PMA process, three devices (no.24, 28, 33) had foreign clinical data, Japanese clinical data were required. Since those indications were for eye diseases, it was supposed that there were ethnicity-associated differences in morphology, such as color, between foreigner and Japanese. As other cases required Japanese clinical data with foreign clinical data, the foreign clinical data were provided as former device (no.32) (Figure 5).

For 12 devices with approval in the USA or EU that required both foreign and Japanese clinical data (Supplemental Figure A.1, no.1-12), the review reports detailed that the Japanese clinical data were used to confirm the suitability of the healthcare environment. For example, for an implantable left ventricular assist device (LVAD, three devices), which is a life support system, Japanese clinical data were necessary to confirm the regional suitability of the operative technique, postoperative care in the hospital, and home care by the patients themselves. Japanese clinical data were also needed for transcatheter heart valves (two devices), to confirm the suitability of the operative technique for implantation of the transcatheter aortic valve, and for three drug-eluting stent devices, to confirm the safety, tolerability, and pharmacokinetics of the drug, safety of antiplatelet therapy for preventing stent thrombosis, and extrapolation of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Japanese data</th>
<th>Japanese data</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
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<td>Approval in the USA or EU</td>
<td>44</td>
<td>45</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Foreign data requiring Japanese data</td>
<td>22</td>
<td>45</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Orphan/priority review/expedited review</td>
<td>12</td>
<td>15</td>
<td>$p = 0.1783$</td>
</tr>
<tr>
<td>Class IV</td>
<td>31</td>
<td>27</td>
<td>$p = 0.5521$</td>
</tr>
</tbody>
</table>

$p$ value: Fisher’s exact test.

Figure 4: Factors affecting the requirement for Japanese clinical data in Japanese approvals.
foreign clinical data (Supplemental Figure A.1). For the four other devices, Japanese clinical data were submitted to confirm the suitability of the operating technique and healthcare environment.

In the review reports numbered 13-19 in Supplemental Figure A.1, no reasons were given as to why the Japanese clinical studies were conducted, and we therefore considered the reasons according to our own judgement. For an implantable LVAD (no.16), a transcatheter heart valve (no.19), and a brain artery stent (no.17), we supposed that the Japanese clinical data were used to confirm the suitability of the high-risk operative technique. With the use of beads for arterial embolization (no.14), the target disease in the foreign study was uterine fibroid where those for approval in Japan were hypervascular tumors including uterine fibroid. For capsule endoscopy (no.13), only Japanese clinical data were used when the data package was submitted, although European clinical data were added during the review process. For an implantable stimulator to control urination and defecation (no.15), foreign data concerning the use of the previous model of this device were insufficient for Japanese approval. Thus, it is suggested that Japanese clinical data were not an essential requirement for submission when foreign clinical data were included in the Japanese data package for approval. As the clinical performance of a medical device is less sensitive to ethnicity than the efficacy and safety of drugs, the performance of a device can be evaluated using foreign clinical data, without additional Japanese clinical data.

However, this idea that medical devices are insensitive to ethnicity did not apply in all cases. Japanese clinical data were required for the Japanese approval for 50% of devices with prior approval in the USA or EU (Figure 2).

This study indicated two reasons why Japanese clinical data were a necessary addition to foreign clinical data. One was that the performance of the device was sensitive to ethnicity, which includes regional differences in the medical environment. For example, for an implantable LVAD, the new implantation techniques, treatment after the operation, and home care requirements were new medical management practices in Japan. Then, clinical data of Phase I, II and III clinical studies were additionally required to evaluate ethnicity-associated differences [15].

Since the development periods for a drug-eluting stent (no.20) and vascular stents (no.21 and 22) were the same in the USA and Japan, the clinical trials were conducted globally.

Thus, most of the requirements for Japanese clinical data were due to the differences in regional medical environments between Japan and the original approving region.

4. Discussion

Although the majority of medical devices have been registered with the Japanese regulatory agency following approvals in the USA or EU, Japanese clinical data were still required in part of the cases. The purpose of this study was therefore to clarify the factors affecting the requirement for Japanese clinical data for approvals of high-risk devices in Japan.

Our results suggest that Japanese clinical data were not an essential requirement for submission when foreign clinical data were included in the Japanese data package for approval. As the clinical performance of a medical device is less sensitive to ethnicity than the efficacy and safety of drugs, the performance of a device can be evaluated using foreign clinical data, without additional Japanese clinical data.

However, this idea that medical devices are insensitive to ethnicity did not apply in all cases. Japanese clinical data were required for the Japanese approval for 50% of devices with prior approval in the USA or EU (Figure 2).

This study indicated two reasons why Japanese clinical data were a necessary addition to foreign clinical data. One was that the performance of the device was sensitive to ethnicity, which includes regional differences in the medical environment. For example, for an implantable LVAD, the new implantation techniques, treatment after the operation, and home care requirements were new medical management practices in Japan. For a transcatheter heart valve, the transcatheter aortic valve implantation was a new operating technique in Japan. For a drug-eluting stent, the safety and similarity of the pharmacokinetics of the eluting drug and the duration and safety of the antiplatelet therapy for prevention of stent thrombosis were confirmed using the Japanese clinical data. Therefore, Japanese clinical data

![Figure 5: Relationships between foreign clinical data and requirements of Japanese clinical data.](image-url)
were necessary to confirm the suitability of the regional operating technique, postoperative care in the hospital, and home care by the patients themselves (Figure 5).

The other major reason why Japanese clinical data were necessary was that a device had undergone improvements from the original device that had been approved in a foreign region. A medical device usually undergoes repeated improvements over its lifecycle. For most of these improvements, clinical data were not required for approval in the USA [16, 17]. Therefore, no clinical data were available for the improved medical devices, although the devices were available for clinical use in foreign regions. In this situation, new clinical data were required for the Japanese approval.

When a global medical device is being developed, its development normally starts in the region with the largest market size. As the Japanese market size is smaller than that of the USA and EU, development for the Japanese market may lag behind.

In contrast to the situation with drugs, as the performance of a medical device is insensitive to ethnicity, extrapolation of foreign clinical data to a new region is frequently allowed. However, it is suggested that, if a simultaneous multi-region submission is not made, the device may undergo improvement, and new clinical data may be required for the new region with a smaller market, such as in Asian countries. New clinical data may also be required to confirm the suitability of a device for regional operating techniques and medical environments.

5. Conclusion

In conclusion, our findings suggest that Japanese clinical data were not an essential requirement for the Japanese data package for approval when foreign clinical data were included. However, there were some exceptions: one was the situation where the performance of a device was sensitive to the ethnicity associated with the medical environment. Another case was where devices had undergone repeated improvements from the original device approved in the foreign region.

It is suggested that, if simultaneous submission is missed, a device may undergo repeated improvements, and then new clinical data are required for approvals in new regions.

6. Declaration of Conflicting Interest

The authors declare no conflicts of interest.

7. Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency.

8. Article Information

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9. References


10. Supplemental Materials