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Promotion of Japan's participation in global clinical trials

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The number of global clinical trials including Japan is increasing but still much lower than those including the USA and Europe. The regulatory requirements for clinical trials have been harmonized among Japan, USA, and Europe, and the quality of clinical trials is kept high in these regions. Xofluza (baloxavir marboxil) for influenza approved in Japan under the SAKIGAKE Designation System is a good example of clinical trials including Japan. To include Japan in more global clinical trials, stakeholders should work more collaboratively, and increase the perception that clinical trials can be conducted appropriately and efficiently in Japan. Further measures for better management of clinical trials should also be developed. These would ultimately lead to improved benefits for patients with timely access to new drugs.

Background

The promotion of global clinical trials is expected to bring better medicinal products to patients earlier in multiple countries. In Japan, measures for the promotion of global clinical trials have been taken, including the implementation of good clinical practice (GCP) standards in alignment with GCP developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the development of guidelines related to global clinical trials, and the offer of regulatory and/or scientific advice concerning the development of medicinal products by the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese regulatory authority. In addition to these measures, recent further globalization of activities by pharmaceutical companies has resulted in increased numbers of clinical trial notifications related to global clinical trials in Japan. In the Fiscal Year 2017 (from April 2017 to March 2018), ~50% of all clinical trial notifications were associated with global clinical trials (Fig. 1) [1].

However, when we searched ClinicalTrials.gov on November 15, 2018, under the conditions of Study Type 'Interventional Studies (Clinical Trials)', Country 'United States', Funder Type 'Industry', Study Start From '01/01/2013' To '12/31/2017' (5 years), we found 14 214 clinical trials in the USA [2]. Among these clinical trials, Europe was included in 3367 trials, and seven European countries were included in more than 1000 clinical trials; Belgium, 1139 trials; France, 1633 trials; Germany, 1865 trials; Italy, 1487 trials; Poland, 1257 trials; Spain, 1843 trials; and the UK, 1781 trials. Japan was included only in 708 trials, which indicates that there is potential to conduct more global clinical trials in which Japan participates.

Here, we provide a brief overview of regulatory requirements for clinical trials in Japan, USA, and Europe, and give an example of a medicinal product that underwent smooth clinical development by including Japan. This information could enable medicinal product developers and researchers to see the benefit of including Japan in global clinical trials, which would ultimately lead to better care for patients in all regions involved.

Regulatory requirements for clinical trials of medicinal product in Japan, USA, and Europe

Table 1 provides a brief summary of the regulatory requirements for conducting clinical trials in Japan, USA, and Europe. In Japan, USA and Europe, a clinical trial proposal must be checked by the relevant regulatory authorities before the trial can be started, and the timeline of the

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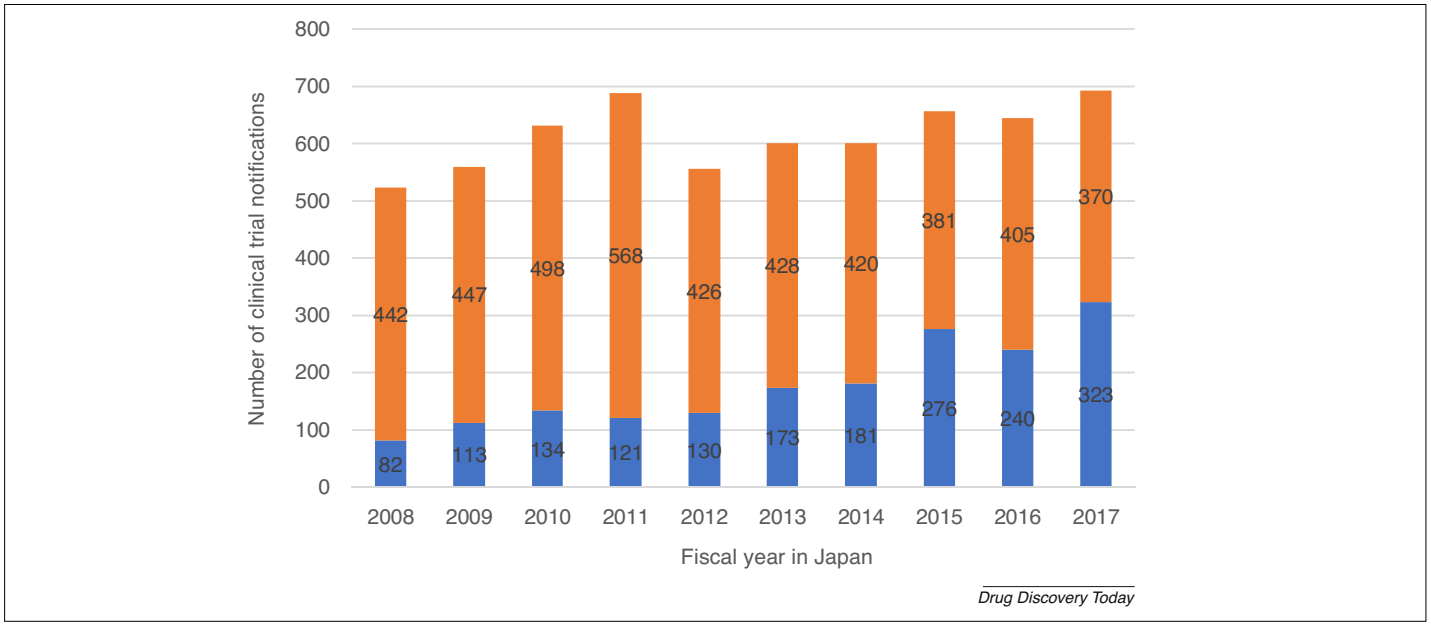

FIGURE 1

Number of notifications of global clinical trials and single in-country clinical trials submitted in Japan from Fiscal Years 2008 to 2017. These notifications must be submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) for review before the trials are started. Blue column shows the number of notifications related to global clinical trials, whereas the orange column shows the number of notifications related to clinical trials to be conducted in Japan alone.

TABLE 1

Summary of regulatory requirements to conduct clinical trials

Requirement	Country/Region (regulatory authority)		
	Japan [13] (PMDA)	**USA [14,15] (FDA)**	**Europe [16] (regulatory authority of European Member State)**
Before starting new clinical trial	Clinical trial notification to PMDA, which checks contents of clinical trial; sponsor can start trial if 30 calendar days pass without any contact from PMDA	Investigational New Drug Application to FDA, which checks contents of clinical trial; sponsor can start trial if 30 calendar days pass without any contact from FDA. However, clinical trials involving exception from informed consent are not permitted to proceed without prior written authorization from FDA	Submission for authorization to start clinical trial: sponsor submits a valid request for authorization to regulatory authority of European Member State in which sponsor plans to conduct the trial. Consideration of valid request for authorization by regulatory authority cannot exceed 60 calendar days
During clinical trial	Trial must be conducted in accordance with standards in alignment with ICH-GCP; safety information should be reported to each regulatory authority within a specified timeline for individual events as well as periodically for complied safety information		
Confirmation of appropriateness for clinical trial conduction by regulator	In general, GCP inspections are conducted by sampling sites, sponsors and so on, during premarket assessment. 'For cause' inspections can be conducted, if needed		

process is clearly specified, being 30 calendar days for both PMDA and the US Food & Drug Administration (FDA). If no communication has been received from the regulatory authorities by Day 30, the sponsor can start the clinical trial without their authorization and/or a permission notice, except for clinical trials involving an exception from informed consent in the USA. In reality, the sponsor might receive inquiries from the PMDA once or twice during the 30 calendar days. In Europe, the application to start a clinical trial has to be submitted to each relevant country, even if the target medicinal product is expected to come under the centralized procedure of premarket application led by the European Medicines Agency (EMA). The timeline of assessment of the clinical trial is 60 calendar days in Europe, but might be shorten by the sponsor receiving the authorization and/or permission notice from the relevant regulatory authorities of European Member States before the 60 days have passed. Normally, regulatory authorities in European Member States issue a decision of authorization in writing for permission to start a clinical trial. Once European Union (EU) Clinical Trial Regulations come into play (the timing of its application depends on confirmation of the full functionality of the EU portal and database) in Europe, the timeline of assessment remains 60 days, but another 31 days are added if the regulatory authority of a European Member State issues inquiries to the sponsor [3].

In addition to the regulator's assessment of a clinical trial before its start, a review by Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) must be done before the start

of the trial in any of the three regions. The review can be conducted in parallel with the assessment by the regulators in Japan and USA. In Europe, the acceptance of such parallel reviews depends on each European Member State. For example, in Japan, the sponsor and sites can sign an agreement on the clinical trial on Day 31 at earliest from the clinical trial notification to the PMDA. Although individual IRBs provide opinions on a clinical trial based on their reviews in Japan and USA, regulatory authorities of each European Member State have established their own procedures to provide individual opinions from ECs per European Member State so that the burdens for EC review process are reduced.

To conduct a clinical trial, ICH-GCP-based standards have been implemented in Japan, USA, and Europe, although the details vary depending on circumstances. For example, roles and requirements for Head of site are specified in Japan. In Europe, each regulatory authority of each European Member State sets different requirements for the conduct of the clinical trial, including collection of consent and ascent in pediatric clinical trials and restriction to collect information on date of birth. Therefore, documents, procedures, and operations of a clinical trial should be modified, including use of local languages, not only in Japan, USA, and Europe, but also in each European Member State. However, a clinical trial can be conducted efficiently within Europe, for example, because only one sponsor or its legal representative should be located within Europe, not per European Member State, and because requirements for manufacturing and releasing an investigational drug are applied at the European level, rather than at the European Member State level.

To ensure the appropriate conduct of a clinical trial, the GCPs of each region specify requirements related to monitoring and auditing. In addition, regulators in Japan, USA, and Europe perform GCP inspections of sponsors and sites. The inspections are normally planned during premarket assessment procedures in each region. This is why the timing of the GCP inspection is predictable, which enables the avoidance of unnecessary burdens for unexpected actions. Furthermore, regulators among European Member States (under the GCP Inspectors Working Group) and regulators among Japan, USA, and Europe (under the GCP Initiative) have collaborative activities related to GCP to reduce inspection burden for sponsors and sites, to improve the efficiency and effectiveness of GCP inspection, and to provide high-quality GCP inspections [4,5].

Example of a medicinal product with smooth clinical development that included Japan

Xofluza (baloxavir marboxil), for treatment of influenza, was the first medicinal product approved under the SAKIGAKE Designation System in Japan [6], in which proactive regulatory supports, including identified contact point with senior managers in PMDA, priority regulatory and/or scientific consultations, and priority premarket assessment, as well as premiums in drug pricing are provided for innovative medicinal products; the development of Xofluza was accelerated by the implementation of clinical trials that included Japan. The drug was approved in February 2018 [6] through a priority premarket assessment with a targeted total time of 6 months [7] in Japan (the targeted total time of normal premarket assessment is 12 months [1]). 'Total time' included not only the premarket assessment and procedural time on the regulator side, but also the time of responses to inquires raised during the premarket assessment on the applicant side. It was also approved in the USA in October 2018 [8]. For the clinical trials for this product, there was a Phase II clinical trial performed only in Japan (T0821 study), a Phase III clinical trial performed only in Japan (T0822 study), and a Phase III global clinical trial that included Japan (T0831 study) [9]. The inclusion criterion for confirmation of influenza infection differed between the T0821/T0822 studies and the T0831 study. In the T0821 and T0822 studies, according to standard care in Japan, patients with positive influenza infection based on the rapid influenza diagnostic test (RIDT) were enrolled. In the T0831 study, because the RIDT is not common in the USA, patients with a diagnosis of influenza infection based on fever and influenza symptoms were enrolled. In addition, influenza infection of enrolled patients was confirmed later by reverse transcription-PCR (RT-PCR) in the T0822 and T0831 studies, and only those patients who tested positive were included in the efficacy analyses.

As a result, more than 25% of enrolled patients in each treatment arm were excluded from the efficacy analyses in the T0831 study because of negative influenza infection based on RT-PCR. In the T0822 study, where both RIDT and RT-PCR were used, only 2.8% of enrolled patients were excluded from the efficacy analyses because of negative influenza infection based on RT-PCR. These results indicate that the clinical trials in Japan supported more efficient development of Xofluza by avoiding the enrollment of extra patients to prepare for the expected many cases of exclusion, given that saving the number of patients enrolled contributes to a reduced burden for both the trial sponsor and the trial sites.

Beyond the case of Xofluza, there could be more clinical development programs where including Japan in a global clinical trial would bring benefits by making available medical environments and clinical practices in Japan. One example might be the clinical development of treatment for an early-stage disease. In Japan, because any patient has easy access to any medical institute at any time and can visit them freely, potential candidates for such a clinical trial can be easily found. Another example might be the clinical development of an anticancer drug, because patients tend to gather in limited specialized hospitals, such as the National Cancer Center Japan. In the case of an orphan medicinal product, medical institutes from across Japan can help identify candidates, because a range of Japanese medical institutes are familiar with clinical trials and can provide high-quality achievements, such as low screening failure rates and fewer deviations from protocol.

Discussion

As described earlier, the regulatory requirements for clinical trials have been harmonized with only small differences occurring among Japan, USA,and Europe, and the quality of clinical trials is kept high in any of these regions. However, to modify the documents, procedures, and operations of clinical trials at a country level, sponsors usually prepare teams corresponding to each region and manage the conduct of clinical trials. Indeed, many Japanese pharmaceutical companies have clinical development teams in the USA and Europe in addition to Japan to coordinate the operations of clinical trials suitably among the three regions. Thus, the need to satisfy regulatory requirements does not differ significantly among Japan, USA, and European Member States.

However, when considering the European Member State level, rather than Europe as a whole, many procedures in clinical trials must be done at the European Member State level; however, the population (potential number of patients) and the market size of medicinal products, significant key factors for the selection of countries in which to conduct clinical trials, are smaller in each European Member State than in Japan [10,11]. Despite the environmental advantage in Japan, the number of global clinical trials differs not only between Japan and the USA and/or European Member States, but also between Japan and each European Member

State. The potential key causes of the differences might be less global clinical trial experience and relatively complicated clinical trial operations in Japan.

In terms of the experiences of global clinical trials, as shown Fig. 1, the number of global clinical trials including Japan has increased since Fiscal Year 2013, which indicates that sponsors and sites in Japan are gaining more experience of global clinical trials. By contrast, in Europe, clinical trials have to be conducted based on the requirements of each European Member State, in addition to benefits that come from the single European market, including centralized premarket assessments by the EMA, resulting in significant experience of clinical trials within multiple European Member States. More experience of global clinical trials at sites not only makes it possible to carry out more efficient clinical trials, but also results in further clinical trial requests being submitted to experienced sites based on their prior performance. The accumulation of such experiences can manifest as the difference in the number of global clinical trials between Japan and each European Member State.

In terms of clinical trial operations, managing a clinical trial tends to be relatively complicated in Japan, compared with the USA and Europe. For example, as described earlier, participation of a broad range of sites, although allowing for many potential patients to be identified, might result in a wide geographical spread of subjects, which would increase administrative costs for the sponsor. In addition, to ensure the high quality of data, the frequency of follow-ups per site, including onsite visits and phone calls, by the sponsor would be relatively high in Japan, even though the regulatory requirements for clinical trials are similar among Japan, USA, and Europe. Unique clinical settings in Japan might be also have advantages and disadvantages. In the case of Xofluza, the RIDT, which is unique to Japan, contributed to an increased accuracy of the influenza diagnosis and reduced the number of patients who needed to be enrolled. However, if a clinical setting in Japan differed substantially from that in the USA or Europe, modification of a protocol would be required to avoid Japan being excluded from global clinical trials.

To address the potential causes of the challenges to including Japan in more global clinical trials, all stakeholders in Japan, including sites, sponsors, and regulators, should make collaborative efforts to develop more successful compounds, such as Xofluza, based on the smooth clinical development that resulted from including Japan in clinical trials. This would also help to increase the perception worldwide that clinical trials can be conducted appropriately and efficiently in Japan. In addition, further measures to improve the efficiency of clinical trial management both within Japan and globally should be taken. For example, leveraging risk-based monitoring and IT technologies could improve efficiency to maintain an appropriate level of quality. Another potential measure might be further regulatory collaboration, including the expansion of Parallel Scientific Advice [12] between the EMA and the FDA, where a developer of a medicinal product can obtain regulatory and/or scientific advice on product development from the EMA and the FDA simultaneously, to include Japan as well as to provide single coordinated advice if applicable. These activities are expected to lower the bar for global clinical trials including Japan, which would lead to benefits for patients without causing the delay of access to drugs for those in the relevant regions.

Disclaimer

The views and opinions in this article are the personal ones of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the organizations with which they are affiliated.

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