Clinical trial disclosure landscape and awareness in Japan

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Abstract
While disclosure of individual clinical study reports (CSRs) is becoming common globally, this is not yet the case in Japan, where the national health authority does not require CSRs to be made publicly available. As CSRs of Japanese studies might be used for marketing applications in other countries and regions, Japanese pharmaceutical companies that would like to expand their market internationally need to prepare CSRs that can be used for global applications and disclosure. In this article, we introduce the current situation in Japan regarding disclosure of clinical study data.

A snapshot of disclosure of individual clinical study results in Japan

In Japan, disclosure of individual CSRs is not required by the national health authority, the Pharmaceuticals and Medical Devices Agency (PMDA). However, individual study results are disclosed in other documents that the PMDA makes available. Other means by which study results are made publicly accessible in Japan include clinical trial registries, publications, and websites of pharmaceutical companies.

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Disclosure on the PMDA website

For a Japanese New Drug Application (NDA), Module 2 (including overviews and summaries) and a part of Module 1 of the Common Technical Document (CTD), as well as the PMDA's review reports, are disclosed on the PMDA website after approval (http://www.pmda.go.jp/PmdaSearch/iyakuSearch/, Japanese language only). As CSRs are located in CTD Module 5, they are not disclosed. The disclosure of documents related to NDAs in Japan is based on the Act on Access to Information Held by Administrative Organs (Act No. 42 of 1999).[1] Under this law, summaries of the PMDA's review tasks related to an NDA are disclosed to the public in order to demonstrate that the approval of the new drug was based on an appropriate evaluation of its effectiveness, safety, and quality of composition.[2]

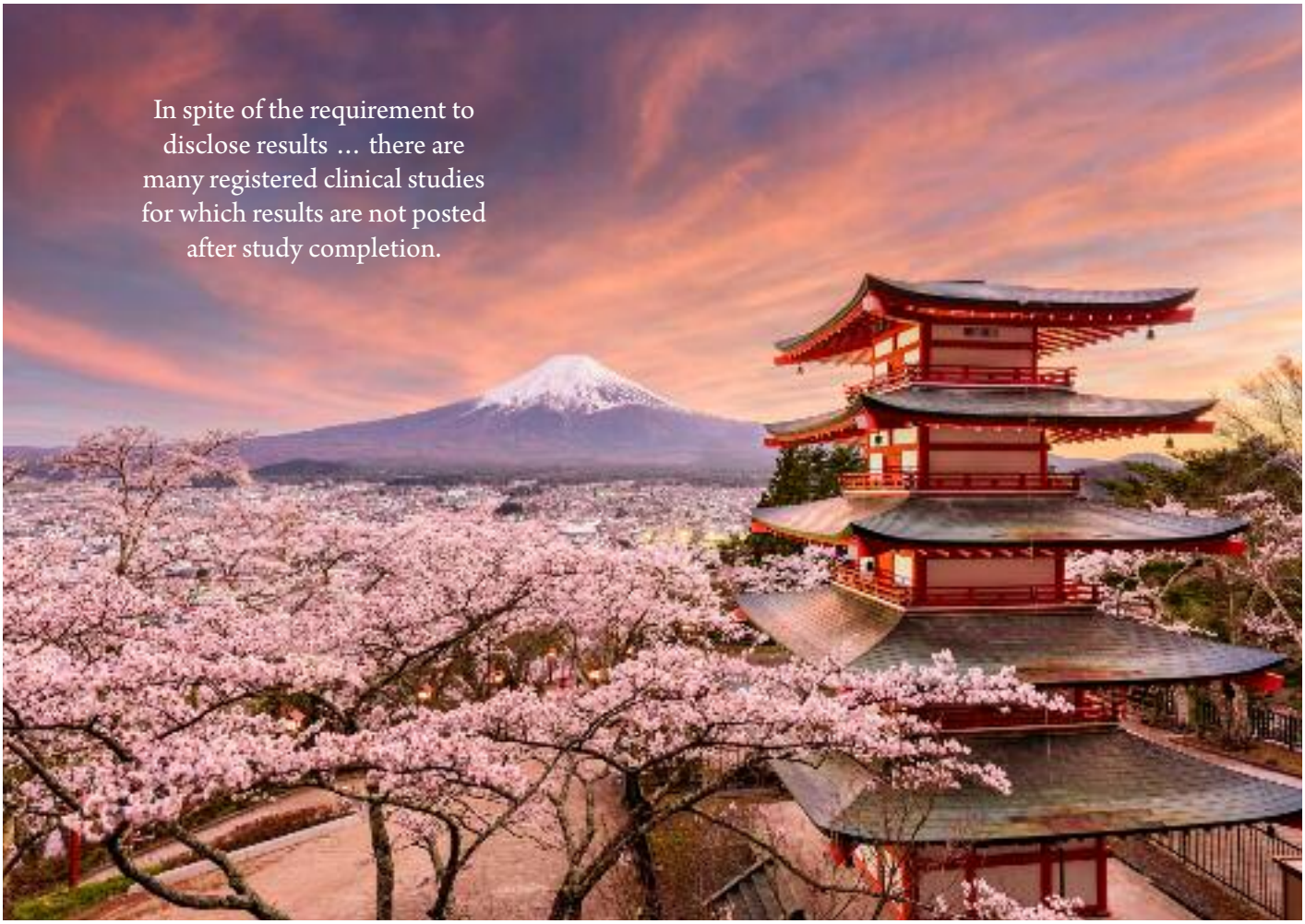
All the disclosed information is prepared in Japanese, with few exceptions. In the disclosed Module 2 of the CTD, the results of individual studies are available, in Japanese, in Modules 2.5 (Clinical Overview), 2.7.3 (Summary of Clinical Efficacy), and 2.7.4 (Summary of Clinical Safety). In addition, Module 2.7.6 (Synopses of Individual Studies) of Japanese NDAs includes more data than the standard ICH E3 synopsis in order to comply with the PMDA's preferences. For Supplemental New Drug Applications (sNDAs), which are filed to update parts of a prior application (e.g., to add a new indication), only the PMDA's review reports are disclosed. This means that the results of clinical studies that support approval of an sNDA are not disclosed, except as summarised in the PMDA's review reports.

Before disclosure on its website, the PMDA asks sponsors to prepare redacted/masked versions of CTD documents and the PMDA's review reports. Sponsors have to show which parts they would like to mask and the reasons (protected personal data or commercially confidential information [CCI]).[3] However, the PMDA may not accept all proposed masking, often disagreeing with the sponsor on what they consider to be CCI.

Disclosure in a clinical trial registry

After three clinical trial registries were jointly named the Japan Primary Registries Network (JPRN) in 2008, registration of clinical studies conducted in Japan increased sharply, with a more than five-fold increase in registrations per year by 2013.[4] This increase occurred after registration before study start became generally required by scientific journals as a prerequisite for publication of results. Another factor in this increase was the added requirement to register interventional trials after a 2008 update (enacted in 2009) of the ethical guidelines for clinical research in Japan by the Ministry of Health, Labour and Welfare.[5] These guidelines were superseded in 2014 by the Ethical Guidelines for Medical and Health Research Involving Human Subjects,[6] which require registration of interventional studies in one of three Japanese registries. Study registration information in Japanese and English is required; the latter may be in an English language registry. As more global and fewer local studies are run in Japan, the proportion of studies registered in ClinicalTrials. gov may increase.

For registered clinical studies, summary results are available in Japanese and English from JPRN registries: Japan Pharmaceutical Information Center Clinical Trial Information (JAPIC CTI, http://www.clinicaltrials.jp/user/ctrSearch_e.jsp), University Hospital Medical Information (UMIN, https://www.umin.ac.jp/ctr/), and Japan Medical Association Center for Clinical Trials (JMACCT, http://www.jmacct.med.or.jp/en/what-we-do/registry.html). English summaries of results may also be provided elsewhere (e.g., ClinicalTrials.gov). Limited data are generally disclosed in registries, including results for the primary endpoint and perhaps the main secondary endpoints. The format of disclosed results is as a brief synoptic summary in JAPIC CTI, the Japanese registry where most industry-sponsored studies are registered. When they are disclosed, study results on UMIN and JMACCT are most often provided as a link to a publication; alternatively, small text-box summaries without tables or figures are posted. In spite of the requirement to disclose results, as described above, there are many registered clinical studies for which results are not posted after study completion.[6]



Disclosure as a publication

Publication of clinical trial results as journal articles has become common globally. However, the publication rate is still low for registered studies.[7] This is also true in Japan. Of over 3,000 studies registered during the first 5 years in UMIN, results were published for only 10%.[8] In a survey of 179 lung cancer studies registered in UMIN, results for approximately half were published, and results were more likely to be published if positive.[9] Results of local studies in Japanese patients are sometimes published in Japanese language journals to inform local healthcare professionals of evidence relevant to the treatment of Japanese patients. The emerging trend towards inclusion of plain language summaries to accompany publications or abstracts to inform lay people has not yet caught on in Japan.

Principles for responsible clinical trial data sharing

Some large pharmaceutical companies have developed their own Japanese websites for posting their clinical study data. The disclosed documents are usually a "public disclosure synopsis" created for the general public, rather than a full CSR. Alternatively, links to clinical trial registration sites are provided. The documents posted on the company websites are usually in English.

In January 2018, member companies of the Japan Pharmaceutical Manufacturers Association (JPMA), which is a member of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), committed to clinical trial data sharing based on the "IFPMA Principles for Responsible Clinical Trial Data Sharing" (http://www.jpma.or.jp/about/basis/rinsyo/policy18.html). It is expected that this policy will promote data sharing by all companies. It includes the following five commitments:

1. Enhancing data sharing with researchers,
2. Enhancing public access to clinical study information (after approval of a medicine or a new indication),
3. Sharing results with patients who participate in clinical trials,
4. Certifying procedures for sharing clinical trial information, and
5. Reaffirming commitments to publish clinical trial results.

Many investigators, health care professionals, and patients who participate in clinical trials believe that sharing data from individual clinical trials might help inform other patients with the same diseases and those who treat them; however, in Japan, the study data are mainly used in NDA dossiers and not otherwise utilised. As Module 5 of the CTD is not disclosed, availability of detailed study information is

limited, especially in regard to study conduct, statistical analysis methods, and results of secondary or exploratory endpoints typically only described in CSRs. And yet this information could be helpful in guiding further research and in clinical practice.

Influence of the approach to CTD content on CSRs used for Japanese NDAs

The approach in Japan regarding CTD clinical content differs from that in other countries in that greater emphasis and focus is placed on the summarised data in Module 2 than on the CSRs. As a result, a more streamlined approach is taken in developing CSRs for NDAs in Japan, to allow deployment of more resources and effort for Module 2.

CTD preparation strategy: Robust Module 2 and concise CSRs

The CTD designates a common format for an NDA, with CSRs in Module 5; however, the way in which they should be written and the content that should be described depends on the country and/or region. As noted above, for Japanese NDAs CTD Module 2 must be prepared in Japanese, except for tables and figures, which may be prepared in English. The PMDA does not simply accept a direct translation of Module 2 documents prepared in English that were submitted to agencies in the US or EU (i.e., the FDA or EMA). As the PMDA seems to place emphasis on Module 2 in NDAs prepared using a Japanese language structure and logic, Module 2 is the established place in a Japanese NDA where claims are developed based on the risks and benefits of the drug. On the other hand, English is acceptable for Module 5. Therefore, most Japanese pharmaceutical companies that develop their product worldwide prepare CSRs in English in the same way as global companies do, even if the clinical studies are conducted only in Japan. Because of the emphasis on discussion of results in Module 2 of a Japanese NDA, the CSR for Japanese studies has become more concise, especially the discussion section, with a focus on quick and accurate preparation.

Presentation of individual clinical study results in Module 2

CTD Module 2.7.6 in Japan tends to be much more comprehensive than a standard ICH E3 CSR synopsis, often being 50 pages and sometimes more than 100 pages per study. In addition, an administrative notice, "Format for Preparing the Common Technical Document for Submission of New Drug Applications to Reduce Total Review Time", issued in 2011,[10] clarified that the safety data from individual clinical studies is to be presented in Modules 2.7.4 and 2.7.6. Therefore, there is a tendency to prepare the CSR synopsis in a way that facilitates efficient CTD preparation, for example by including enough information or data to meet the PMDA's requirements for Module 2.7.6, especially when CSRs are prepared in Japanese.

Importance of preparing a CSR to meet global requirements

Since there is no requirement to disclose CSRs in Japan, the interest of pharmaceutical companies is focused on preparing what is necessary or sufficient, and to reduce effort for CSR preparation. In global companies, local studies conducted only in Japan are becoming less common. In addition, because English is acceptable for CSRs in Module 5 of Japanese NDAs, pharmaceutical companies typically select English as the language for CSRs of Japanese clinical studies so as to avoid preparing CSRs in two languages should they be used for marketing applications in other countries or regions. As they are generally prepared in English, it would be productive if CSRs were written by native writers of English. Opportunities for Japanese writers to prepare CSRs have been decreasing, and writers seem to be less interested in CSRs and the changes in circumstances surrounding CSRs. However, Japanese pharmaceutical companies that would like to expand internationally need their writers to prepare CSRs that can be used for global applications and disclosure. CORE (Clarity and Openness in Reporting: E3-based) Reference (http://www.core-reference.org/)[11] is a useful tool that can be used by Japanese writers in preparing CSRs for global use; it provides timely information on the global environment surrounding CSR preparation, with consideration for disclosure after marketing approval. However, survey responses from 25 JPMA companies in 2016 showed that none were using CORE Reference and 72% were not at all familiar with it, although all expressed interest in learning about it.[12]

Conclusions

It seems certain that the number of CSRs for Japanese studies that are publicly disclosed is increasing, due to the fact that CSRs are often used for applications in multiple countries and regions. Other types of clinical study data disclosure, such as clinical trial registration websites and publications, are also currently promoted in Japan. However, the possibility remains that some clinical study data may remain undisclosed, perhaps in cases of clinical studies which were not used for an NDA and drugs for which marketing approval was not obtained or clinical development was terminated. We hope that disclosure of clinical trial data will be promoted in Japan, to fulfil an ethical commitment to patients and researchers and to promote advances in medical treatment.

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The opinions expressed in this article are the authors' own and are not necessarily shared by their employer.

Conflicts of interest

The authors are employed by ProScribe Medical Affairs, Envision Pharma Group, which provides medical writing services to client companies in Japan and other countries.

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