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China PASS and Japan PMS

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ABSTRACT

In 2017, China Food and Drug Administration (CFDA) participated as a member of the International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). In 2018, CFDA changed its official English name to National Medical Product Administration (NMPA), and new system was created in which drugs are managed separately from foods.

In addition, policies to promote the import of drugs have been successively published. These have included shortening of the period of approval for Chinese import reviews of drugs manufactured overseas, and establishing a special channel for review approval operations on overseas new drugs that are urgently needed in clinical practice. As a result, the study data for new drug applications has been insufficient to assess the safety of the drug. Accordingly, requests for submission of post-marketing data have been gradually increasing.

When the drug has been marketed in Japan or Hong Kong, Macao, and Taiwan regions with sufficient clinical trials or actual clinical cases, the applicants can submit clinical data on drug use in those countries and regions with relevant analysis, and do not require research data on ethnic differences. Additional confirmation on safety/efficacy is expected to obtain from the following post-marketing. Therefore, attention to post-marketing has been increasing.

Chinese post-marketing data collection system is similar to Japanese system. This paper introduces the post-marketing data collection system, and its data collecting process in Japan. Also introducing the current trial collaboration between China and Japan.

INTRODUCTION

Japanese Health Authority (J-HA) obligates pharmaceuticals manufacturers to conduct a surveillance after approval to re-examine the efficacy and safety of the drug, which is called Re-examination System. Accordingly, Japan pharmaceutical companies have huge amounts of patient data on the drug efficacy and safety under actual clinical circumstances.

In Japan, this surveillance is called Post-Marketing Surveillance (PMS), and PMS should be conducted under the specific regulation, Good Post-Marketing Study Practice (GPSP). GPSP is different from Good Clinical Practice (GCP), for example, obtaining informed consent (IC) is not required in GPSP.

JAPAN SITUATION

RE-EXAMINATION SYSTEM

After a drug approval (including approval of partial changes in indication), J-HA designates the re-examination period, generally eight years. However, in many cases, J-HA designates four years if the approval is on the additional indication, and ten years on orphan drugs.

Figure 1 shows an overview of Re-examination System.

Marketing Authorization Holder (MAH) must collect and analyze the post-marketing safety and efficacy data and report to J-HA regularly during re-examination period. After re-examination period, MAH must analyze all post-marketing safety and efficacy data, and submit the re-examination application dossier to J-HA.

If PMS data is included in the re-examination application dossier, MAH will be subject to GPSP inspection from J-HA. The J-HA inspector will review that PMS has been conducted complying with GPSP.

After the GPSP inspection, MAH will receive the notification of the results of re-examination from J-HA and the re-examination process will be complete.

There are three types in the notifications of re-examination result.

- Withdrawal of approval
- Elimination or modification of indication
- No actions in particular

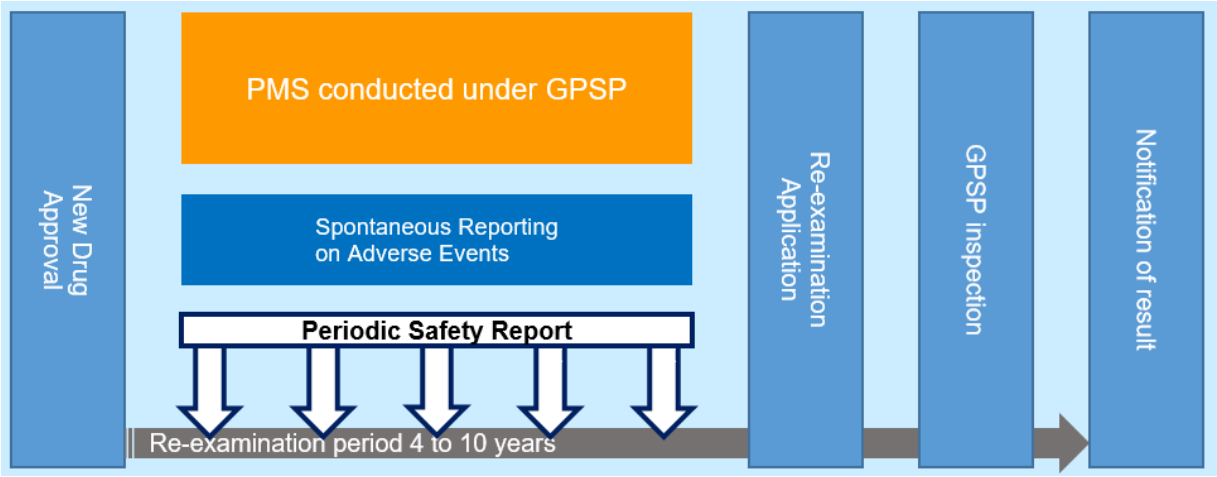

Figure 1: Overview of Re-examination System

PMS

Protocol preparation

Main purpose of PMS is to collect and validate information on the safety and efficacy (primarily focus on safety) of a marketed drug and re-evaluate the approval decision. PMS is considered to be necessary for the following reasons.

- Small number of patients have been involved in clinical trials.
- Medical practice of the drug in clinical trials is not same in the actual clinical circumstances.

Figure 2 is a general process for developing protocols for PMS. Following a new drug application, MAH prepares a draft protocol and case report form (CRF), and submits it to J-HA. J-HA requests MAH to answer some queries about their PMS plan if needed. After that, MAH prepares their final protocol and CRF, and submits it to J-HA for approval. Then, MAH starts to collect PMS data under the protocol and GPSP.

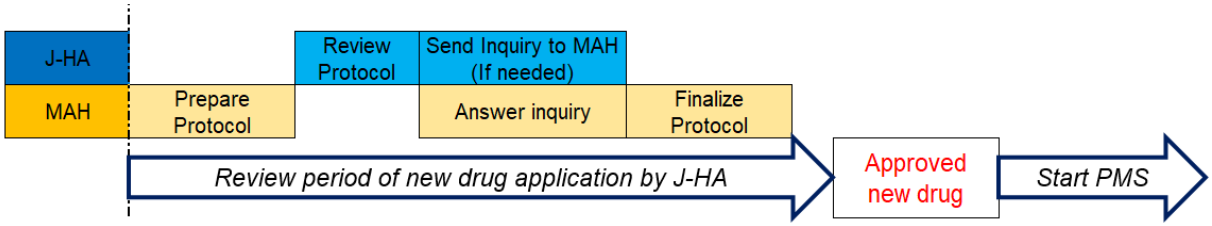

Figure 2: Process of protocol development for PMS

Data collection

Figure 3 is a general process for collection of post-marketing data.

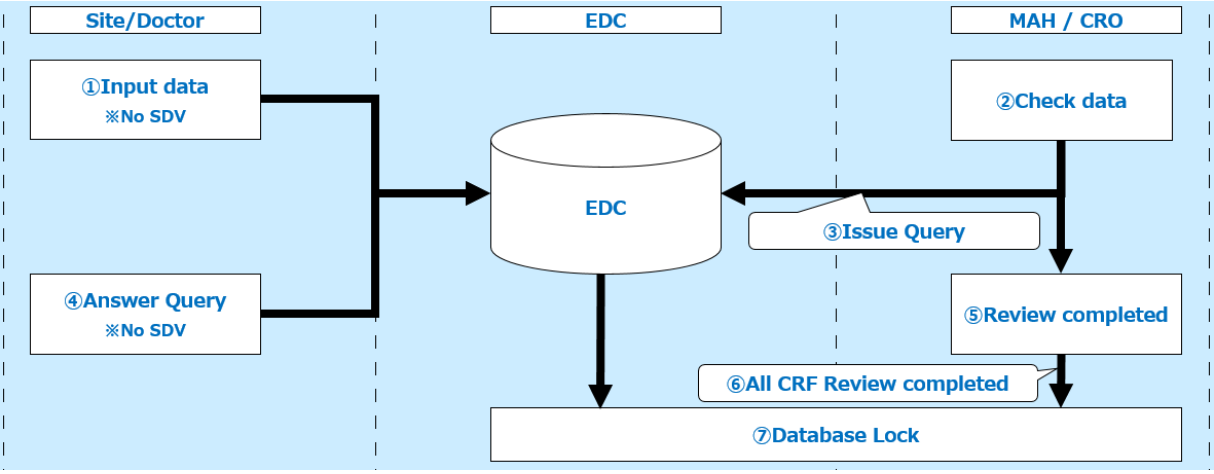

Figure 3: Process of collecting post-marketing data

The process is very similar to clinical studies however some processes are different.

- Obtaining IC is not required in PMS regulation.
- Source Date Verification (SDV) is not allowed in PMS regulation.
- Doctors normally cannot get the support from Clinical Research Coordinator on CRF completion.

Table 4 shows the data items generally collected in PMS. The scope is also very similar to clinical studies. Sample size ranges from a small number to a few thousand patients or all patients, depending on the protocol. The data capturing system is mostly Electronic Data Capture (EDC). In some cases, for example, if the doctor participating all-patients surveillances cannot use EDC by specific reasons, paper CRF will be used.

Scope of data	Ex.
Demography	sex, age
Diagnosis	diagnosis date
Medical history	medical history term
Dosage administration record	total daily dose, start date, end date, reason for dose change or discontinuation
Prior and concomitant medications	name of medication, reason
Efficacy	Ex. Best overall response
Adverse events	Event name, start date, end date, outcome, serious or not, relationship to study drug

Table 4: Scope of data collection for post-marketing surveillance

Periodic Safety report

MAH should periodically tally all drug-related information from PMS and spontaneous reported AEs, then report them to J-HA during the re-examination period. Figure 5 gives an overview of a periodic safety reporting system.

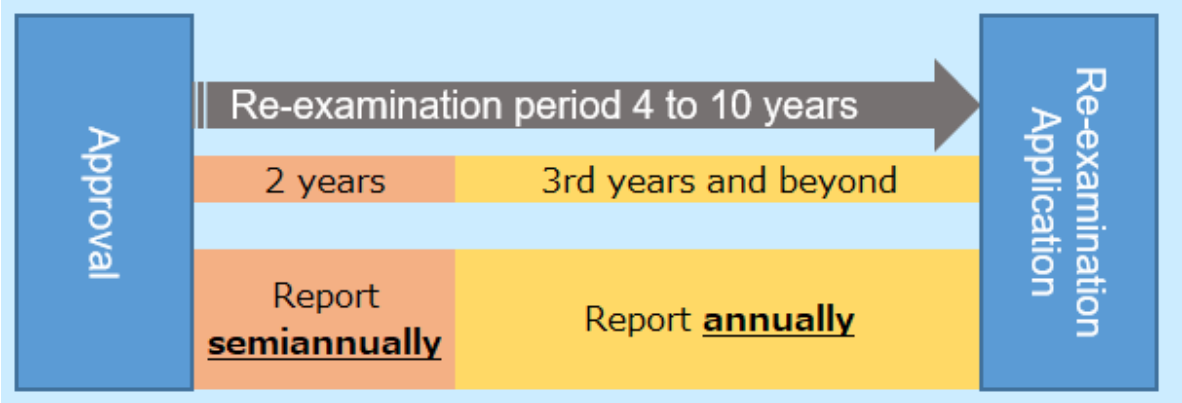

Figure 5: Overview of periodic safety reporting system.

MAH should report the drug use-results to J-HA semi-annually in the first two years after approval, and annually thereafter.

CHINA SITUATION

REGULATION CHANGES

The clinical development environment in China has recently seen drastic changes. China FDA participated as a member of the ICH in 2017. In 2018, China FDA changed its official English name to NMPA. In addition, regulatory reforms have been introduced quickly. Table 6 is a highlight of regulatory reforms in China.

2018/07/10	接受药品境外临床试验数据的技术指导原则
2017/12/28	关于鼓励药品创新实行优先审评审批的意见
2018/08/08	关于征求境外已上市临床急需新药名单意见的通知
2018/10/30	关于临床急需境外新药审评审批相关事宜的公告

Table 6: Highlight of regulatory reforms in China.

China FDA has announced new special channel to approve new pharmaceuticals in which urgent clinical needs. MAH can submit an application directly through this special channel without conducting clinical trials in China, whenever meeting the condition of urgent needs. The application should include overseas clinical trial data with an analysis of ethnic differences. MAH must confirm that the drug is safe and effective for use in China. China FDA has announced that if the drug has already been marketed in Japan, Hong Kong, Taiwan, and Macau, it will be exempted from the ethnic differences analysis requirement.

It is likely that post-marketing safety and efficacy data will weigh heavily in China for these cases. Post-authorization safety studies (PASS) will likely continue to increase in the future.

CHINA PASS

PASS is a post-marketing data collection system in China. It has been increasing in China every year. PASS is similar to PMS in some respects such as study design (Single-arm, Non-intervention), primary objective (Safety), in the present situation, but policies and guidances for PASS are still not as comprehensive as Japan PMS. Actually, the basis of China PASS has been evolving every year. NMPA will set an observation period for new drugs upon approval. NMPA designates MAH to conduct PASS during the observation period in many cases. In that case, MAH prepares PASS protocol and CRF to collect post-marketing data as non-interventional way (without imposing any diagnostic/therapeutic procedure, or visit schedule) in order to evaluate the safety of the drug under actual clinical practices. The duration of the observation period is generally at longest five years from the drug approval date. During this period, the drug patent is protected.

COMPARISON BETWEEN CHINA PASS AND JAPAN PMS

Conditions of China PASS are similar to Japan PMS. Table 7 is comparison of current situation※ between China and Japan.

※As of July 16, 2019

	China PASS	Japan PMS
Study design	Single-arm, Non-intervention	Single-arm, Non-intervention
Primary objective	Safety	Safety
Observation period	At longest 5 years	4 - 10 years
Patent exclusivity	Yes	Yes
Periodic safety report	Annual	Annual / Semiannual
Inspection by health authority	No	Yes

Table 7: Comparison between China PASS and Japan PMS.

COLLABORATION BETWEEN CHINA AND JAPAN

It is the right moment to collaborate between China and Japan in this post-marketing area. As mentioned above, there already have been massive experiences of post-marketing in Japan, and position of post-marketing data of China will become increasingly important. Especially in global pharma companies, collaboration between China and Japan affiliates seems to generate maximum effect.

We have already started discussion between the China PASS team and the Japan PMS team that focused on data management and data standardization in our company. We started from documents sharing such as Japanese Standard Operating Procedures for PMS, data management documents (Data Management Plan, Edit Checks Specification, Standard Case Report Forms).

If we can collect Chinese post-marketing data and Japanese post-marketing data in the same format, using the same processes, we can then share information and engage in discussion from a similar perspective. In this way, it will improve operational speed, operational efficiency, and data quality in post-marketing field. There will be an advantage for new drugs approval strategy if we can marge Chinese and Japanese post-marketing data in the future.

CONCLUSION

The pace of change in pharmaceutical regulation/new drug development environment is rapid. Though there are many unknown facts or hurdles on how to collaborate between China and Japan in this post-marketing field, the standardization of post-marketing data and the process between China and Japan will contribute to new drug development each other, leading to mutual benefit in future. We can say that it also would be beneficial to both countries' patients.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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