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REGULATORY PROVISIONS FOR NEW DRUG REGISTRATION IN JAPAN

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ABSTRACT

Regulatory affairs is a department that is responsible to protect the public health by controlling the safety and efficacy of the product. RA deals in an area like pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemical, cosmetics, and complementary medicines. New Drug Registration is a medium through which the sponsors provides that the regulatory authority has approved a new pharmaceutical product for sale and marketing. Registration provides the information of drug and allow the regulatory agencies to ensure the benefits exceeds the risk. Different countries have their own registration process following their own guidelines and provisions. This review particularly focuses on the registration process followed in Japan. Beyond language obstacles, Japan's drug approval and review procedure is simpler and less complicated than in some other nations. The PMDA offers sponsors counselling to help them understand the requirements and the step-by-step process for drug approval, in addition to regulatory aspects. Because of this, a lot of manufacturers select Japan as their drug market. One of the biggest markets in the world for pharmaceuticals is Japan. According to data from the Ministry of Health, Labour, and Welfare; the market value, which includes over-the-counter drugs is about $95 billion (MHLW).

Keywords: PMDA: Pharmaceuticals and Medical Devices Agency, MHLW: Ministry of Health, Labour and Welfare, CTD: Common Technical Document, ICH: International Council for Harmonization, RA: Regulatory Affairs

INTRODUCTION

According to Pharmaceutical and Medical device Agency (PMDA), New Drug is defined as new dosage form, novel API or new formulation being prepared for human use.

Pharmaceutical and Medical Device Agency (PMDA) is regulatory authority of Japan. For marketing of new drugs in Japan, it is mandatory that drug is registered along with marketing authorization to PMDA under new drug category. MHLW is also involved in this process to some minor extent. PMDA handles ADR, review and safety measures of Pharmaceuticals and Medical Devices.

The objective of this article is to provide the detailed knowledge of the registration process in Japan as well as helps the authorities and sponsors to check the safety and efficacy of the pharmaceutical products.

CLINICAL TRIAL PROCEDURE

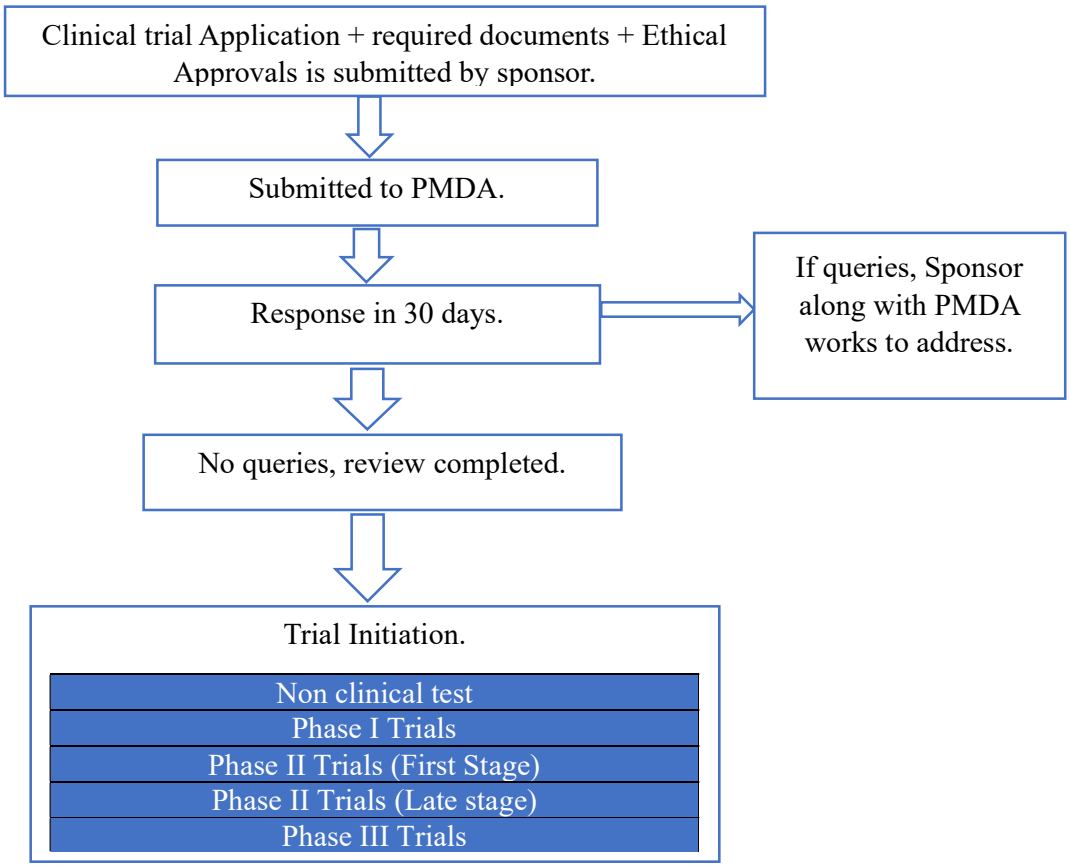

Figure 1: Clinical Trial Procedure

Information about adverse reactions and infections during research:[1]

As stated in "Clinical Safety Data Management", safety information received during the trial must be submitted quickly. The requirements to describe ADR, etc. pertaining to the investigational product to the Minister was outlined by law in the

revision of the Enforcement Regulations of the Law made in 1997 for which the ICH guidelines worked as a reference. The following describes the rules:

A: Weekly reporting

a) Demise

b) Situations (fatal)

B:15-Day reports

a) Any of the mentioned occurrences, which are not anticipated from the investigational product's detail in the investigator's brochure, are suspected of being brought on by an adverse reaction to investigational product in question that may have been brought on by the investigational product in question.

• Any situation that necessitates hospitalization for treatment or lengthens the hospital stay.

• Disablement

• Situations that might lead to disability

• Another life-threatening illness

• Congenital disorders or diseases in the upcoming generation

b) Deaths that are anticipated or circumstances that could cause death.

c) Actions taken in response to the experimental product's safety issues, such as ceasing export sales or manufacturing in another nation.

d) Studies demonstrating the potential for the investigational product in question to result in cancer or other serious diseases as a result of adverse reactions, etc.

Interview advice meeting:

To enhance and reinforce the calibre of clinical research, the PMDA has set up a framework for protocol consultation. The Review Department's teams that handle consultations and reviews have been combined. Improvements have been done in the quality of consultations with regard to consultation, implementation, and compilation of records as efforts to fulfil the needs of people requesting consultations due to the rising demand for clinical trial consultations. The PMDA's important points of discussion during this meeting are listed below. The following PMDA homepages provide information on the items for consultation, the most recent update on fees of consultation, and the application process for interview advice meetings.

Approval review

"Approval Applications for Drugs," specifies the documents that must be submitted with each application category. The PMDA offers data on clinical quality and safety for CTD in the standard format.

The PMDA is primarily in charge of the process involved in a new drug's approval evaluation. The review staff conducts a thorough team review after PMDA receives the application form.

The time frame after submitting an application for the approval of a new drug is stated in the notice titled "Timeline for Completing the New Medicine Application

Review under the Standard Process. 'The regulatory agencies' and 'applicants' efforts are expected to shorten the PMDA review period for new drugs.

The following are the important points:

A. **Handling of data from long-term clinical studies:** Data on the fulfilment of medication to all subjects for at least six months should be collected as application data. The amended draught of the CTD and the final report, which contains information on how all patients were administered to for at least a year, should be submitted as soon as feasible. It must be filed no later than six months before the complete targeted Period for PMDA review.

B. **Handling of data from long-term stability studies:** At the latest, six months prior to the conclusion of the entire PMDA review period and additional data (including data necessary for determining the planned expiration period) should be presented as a final report. When data were submitted to the Committee, any additional data acquired thereafter should be submitted.

C. **Factors to approach when using a DMF:** Factors to consider when communicating effectively with the person registering the Master File, verifying the Master File registration requirements, and speedily submitting registered Master File information that matches Module No. 2 of the CTD after a product approval application has been submitted.

D. **Application for GMP compliance inspection:** If the applicant determines that an inspection is likely to take place based on a commitment from the inspection department, they apply for inspections of the relevant amenities and make preparations for receiving inspectors at the locations.

- **Compliance review:**
  Following the submission of approval requests, compliance reviews are conducted. They include both on-site and written reviews.
- **Paper reviews:**
  When the applicant submits data to the PMDA as proof for approval reviews, paper reviews are carried out in accordance with "the Guidelines for Paper Compliance Review for New Drug Approval Application Data" of the Evaluation and Licensing Division, PFSB. To inspect such data, Agency officials may, however, go to locations where

source and application data are archived as needed ("on-site inspection"). The examination is mostly carried out by evaluating approved application data brought into the PMDA.

On-site reviews:

In these reviews, the PMDA review team assesses the data at the places where it was gathered or generated. The manual for on-site GCP compliance checks is called "Inspection Procedures for the On-site Verification of GCP Compliance for Drug Application". Reviews are typically conducted in the applicant's offices, facilities, and the clinical study sites (four facilities are typical for novel pharmaceuticals; two facilities are typical for additional indications or orphan drugs). The number of participants in clinical trials and the dates of earlier GCP evaluations should be taken into account when choosing review facilities.

- **GMP compliance inspection:**

Individual drug formulations must receive formal approval before being marketed in Japan. Before a product can be put on the market, the Minister of the Ministry of Health, Labour & Welfare must formally approve it. To do this, data and documents must be submitted for the necessary evaluation of the product's quality, efficacy, and safety. To determine whether the product in the application is a drug that can be marketed by someone who has been granted a marketing business licence for the kind of drug in question, as well as to confirm that it was produced in a facility that complies with GMP standards, it must be examined. As a result, GMP compliance is required for the production and distribution of pharmaceuticals. The Minister of the Ministry of Health, Labour & Welfare minister may refuse to issue a licence to a manufacturing facility that doesn't follow GMP guidelines.

GMP Compliance Reviews:

The plant must be examined by the authorities when a request for a new drug production and marketing approval is made to make sure it truly conforms with GMP requirements. First, the following conditions are used to assess each product's conformity with GMP standards for each component in the provisions and design and facility regulations.

Evaluation rank criteria:

A – Compliance

B - Slightly defective

C - Moderately defective

D - Seriously defective

Global Harmonization of GMP:

Japan has concluded memorandums of understanding (MOU) for GMP approvals with nations that have comparable GMP standards. By accepting each other's GMP inspection findings and exchanging data on drugs marketed in each nation, The purpose of these agreements is to guarantee the standard of medications imported into Japan. With Germany, Sweden, Switzerland, and Australia, these agreements have been reached. The first MRA of drug GMPs with European Union nations was reached in 2003. To ensure greater international standardization and conformity in GMP inspections, it was advised to make effective use of the GMP regulations found in the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

Rules for the Management and Quality Control of Imported Drugs:

Rules for manufacturing control and quality control are set forth in Import Monitoring and Quality Management of Drugs and Quasi-drugs when importers and MA holders import drugs. because it is crucial to ensure that imported drugs are of the same high

quality as drugs made in Japan, but since import business licences have been incorporated into the manufacturing/marketing business licences, this was a problem. These rules contained details that the importer had to agree upon with the manufacturer in the foreign country in line with the agreement.

DATA REQUIRED FOR APPROVAL APPLICATIONS:

The basic notification headed "Approval Applications for Drugs" specifies the information that must be attached to drug approval applications:

Module 1: Administrative information such as application forms and prescribing information

(1) Application documentation table of contents (including Module 1)
(2) Approval application (copy)
(3) Certificates
(4) Status of Patent
(5) Origin, discovery, and development
(6) Conditions of use in foreign countries
(7) Related products list
(8) Package inserts
(9) Non-proprietary name documents
(10) Data for review of poisons, deleterious substances, etc.
(11) Risk management plan
(12) Attached documents

Module 2: Data summaries

(1) Modules 2 to 5 (table of contents)
(2) Introduction of CTD
(3) Quality overall summary
(4) Nonclinical overview

(5) Clinical overview

(6) Nonclinical summary

(7) Clinical summary

Module 3: Quality

(1) Module 3 table of contents

(2) Data or reports

(3) Literature references

Module 4: Nonclinical study reports

(1) Module 4 table of contents

(2) Study reports

(3) Literature references

Module 5: Clinical study reports

(1) Module 5 table of contents

(2) Tabular listing of all clinical studies

(3) Clinical study reports

(4) Literature references

GUIDELINES CONCERNING DRUG APPROVAL APPLICATIONS:

Nonclinical Studies:

1) Guidelines on specifications, physicochemical properties and tests methods **[2]**

2) Guidelines for stability tests **[3]**

3) Guidelines for toxicity tests

4) Good Laboratory Practice (GLP)

5) Guidelines for general pharmacological studies **[4]**

6) Guidelines for pharmacokinetic studies **[5]**

Clinical Studies:

1) Guideline related to Quality of investigational products

2) Guideline related to phases of clinical development

Phase I (clinical pharmacology)

Phase II (therapeutic exploratory)

Phase III (therapeutic confirmatory)

Phase IV (therapeutic use)

3) Guideline related to Studies concerning new dosage regimens, new indications, etc.

4) Guideline for Special considerations

I. Studies of drug metabolites

II. Drug interactions

III. Special populations

IV. Micro dose studies

DRUG APPROVAL SYSTEM

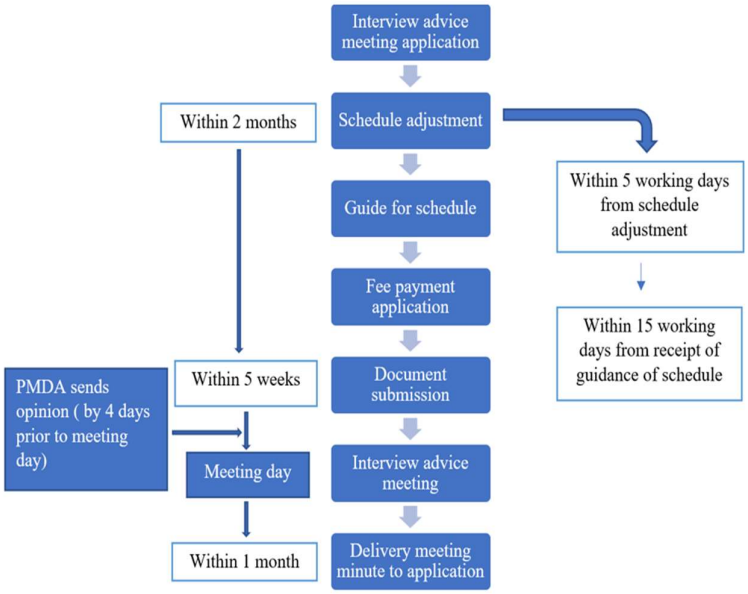

Figure 2: Procedure of Interview Advice Meeting

Form of clinical trial notification along with clinical research protocols submitted within 30 days of the trial's start date for medications needed urgently to avoid diseases that have a significant impact on the patient's health.

Documents to be attached for the first notification

- Justification documentation outlining the reasons the clinical research request was considered to be rational from a scientific standpoint.
- Clinical trial protocol
- The informed consent form and informational materials.
- A case report form sample (CRF)
- Investigator Brochure

Documents to be attached from the second notification

- Documents that detail why the request for a clinical trial was found to be of scientifically reasonable, as well as the informational materials and consent form that were used to obtain informed consent.
- Clinical trial procedure.
- A case report form sample (CRF)
- The most recent investigator's brochure

Format of documents submission

- Report on the clinical research strategy that is separate from the report under inquiry for 30 days.
- The notification must be sent in two copies: one of the original and the other.
- A single XML file and a single PDF file for use in managing information on electronic media.

NEW DRUG APPLICATION (NDA):

Procedure: The PMDA handles the full approval review process, including inspections linked to reviews, advice on clinical trial results, and review work. The PMDA receives applications for medication marketing authorization. Review teams of the PMDA conduct a compliance assessment of the application data, GCP on-site inspection, and detailed review when the agency receives application forms for novel drug marketing authorization. The team then creates a review report. Members of the review team and experts gather to address significant issues as part of the approval review process. Following the expert meeting, a general review conference is held in which team members, subject matter experts, and applicants' representatives participate regarding persons who participated in clinical trials submitted as application data, it is necessary to submit a "list of persons involved in compilation of attached data".

PMDA review process

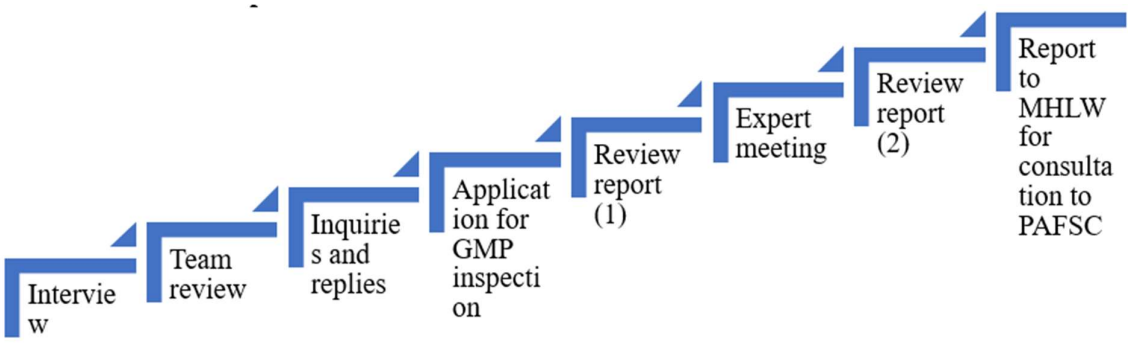

Figure 3: PMDA Review Process

The applicant will also have a year allowed to them, resulting in a total time between the application and commercialization permission to no more than two years. This is in addition to the MHLW's standard approval review time of 1 year beginning on April 1, 2000 (dated March 28, 2000). The MHLW requests that the applicant withdraws their application in the event that it takes longer than expected to respond to their questions or complete further research**.** A document entitled "Points to Consider in Applications for Shortening the PMDA Review Period for New Drugs" was released in June 2010. In order to meet the 2013 target PMDA review times of 12 months for regular reviews and 9 months for priority reviews, this document provides considerations from the applicant's perspective. The Ministry has further demonstrated that the typical review timeframe for new drug applications results in a average overall review period of not more than year for novel drugs. On the PMDA website, you can find information on the typical review period for new drugs.

Drug review:[6, 7]

To evaluate the quality, pharmacology, pharmacokinetics, toxicology, clinical implications, and biostatistics of the specific drug under review. Drug applications are reviewed by a group of PMDA reviewers with backgrounds in pharmaceutical research, physical science, medicine, veterinary medicine, biostatistics, and other fields.

To guarantee that reviews are conducted more successfully by utilizing their advanced expertise, reviewers interact with external experts during the review process. Additionally, PMDA participates in ICH and actively incorporates the standards established at ICH into its drug reviews. ICH stands for the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

By establishing goal review times, PMDA aims to expedite the review procedure while also defining the standards for review by posting the fundamental guidelines for reviewers on its website.

In addition to brand-new medications, PMDA also evaluates generic medications, over-the-counter (OTC) medications, "behind-the-counter (BTC)" medications (requiring pharmacist guidance), and quasi-medications. Additionally, the PMDA re-examines and re-evaluates approved pharmaceutical items.

Process of starting to analyze the data:

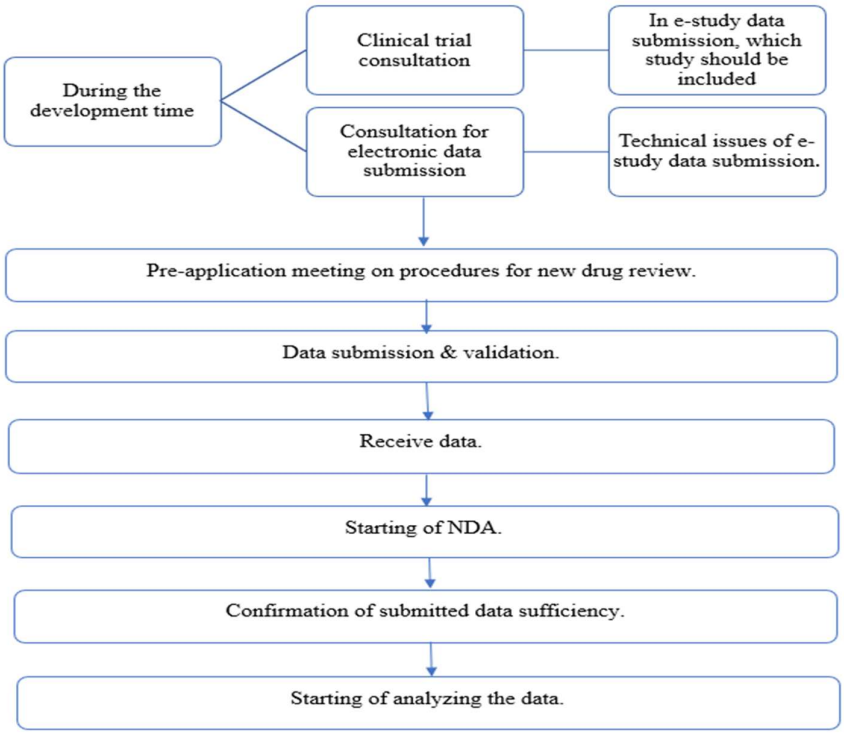

Figure 4: Process for analyze data

Review process & data analysis:

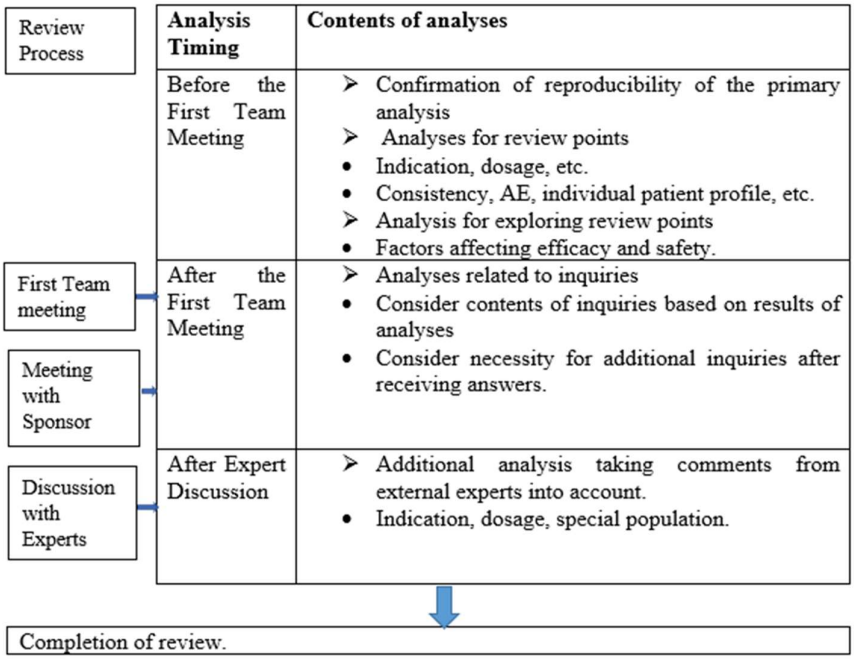

Figure 5: Review process and data analysis

CONCLUSION:

PMDA offers sponsors counselling to help them understand the requirements and the step-by-step process for drug approval, in addition to regulatory aspects. Because of this, a lot of manufacturers select Japan as their drug market. In recent years, the Pharmaceuticals and Medical Devices Agency (PMDA) has given its approval to hundreds of new medications. In order to discover the first-in-the-world approvals and understand the present medication lag, we looked backward at the new drugs that were approved in Japan from 2008 to 2019. The terms "new drug" and "drug lag" were used to refer, respectively, to drugs with new active ingredients and drugs whose international and Japanese clearance dates varied. In the last 12 years, there were 400 new pharmaceuticals approved in Japan, of which 80 (20.0%) were originally approved there, and 320 were approved elsewhere (the United States: 202, or 50.5%; Europe: 82, or 20.5%; other regions: 36, or 9.0%). The remaining 355 have received worldwide approval in both Japan and other countries, while 45 additional medications are still awaiting approval outside of Japan. Utilizing study data in future perspective to analyse new drugs, will improve prediction of efficacy and safety, review M&S findings, and examine cutting-edge evaluation techniques and Ability to make decisions quickly and wisely.

Utilization of collected study data:

- Active M & S.

- Evaluation of novel analysis techniques based on the collected data.
- Meta-analytic experience.
- Effective creation of new drugs:
- Making use of consultation meetings based on cross-product data provided by PMDA.
- Making use of M&S actively.

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