7 December 2020, CMC Strategy Forum Japan 2020

PMDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

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The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA

Outline

- Outline of the bill for the partial revision of PMD Act
- Designation of Pioneering Drugs
- Operations of Conditional Accelerated Approval
- Post-Approval Change Management Protocol (PACMP)
- Management of Regulatory Review of Drugs for COVID-19

OUTLINE OF THE BILL FOR THE PARTIAL REVISION OF PMD ACT

Outline of the bill for the partial revision of PMD Act (Published in 2019/12/4)

- Intent of the revision

  Review the systems in order to provide excellent pharmaceuticals and medical devices that meet people's needs safely, quickly, and efficiently and to develop environments so patients can use drugs with peace of mind in familiar communities.

  1. Improvement of the systems from development to post marketing in order to provide pharmaceuticals and medical devices safely, quickly, and efficiently
  2. Review of the roles of pharmacists and pharmacies so patients can use drugs with peace of mind in familiar communities
  3. Establishment of regulatory compliance systems to gain trust
  4. Others
     - Establishment of a pharmaceutical evaluation and monitoring committee that evaluates/monitors the status of measures to ensure the safety of medicinal products and prevent the occurrence of health hazards
     - Easing of restrictions on blood sampling based on the advancement of science and technology

Outline of the bill for the partial revision of PMD Act (Published in 2019/12/4)

1. Improvement of the systems from development to post marketing in order to provide pharmaceuticals and medical devices safely, quickly, and efficiently

i. Legislation for the “SAKIGAKE Designation System”, priority reviews for drugs for specific purposes, including pediatric dosage and administration

ii. Legislation for the "Conditional Accelerated Approval"

iii. As for changes in the manufacturing methods for drugs that will not affect the efficacy or safety of finished products, a notification can be submitted instead of an application for approval if the change is made according to a plan acknowledged by the MHLW beforehand

iv. Introduction of an approval process for medical devices to appropriately respond to continuous improvement in performance or technological innovations by AI, etc.

v. Making it a general rule to electronically provide package inserts so as to give medical practitioners the latest information on the proper use of products as soon as possible

vi. Mandating bar code labeling on the drug package to enhance the traceability, etc.

Outline of the bill for the partial revision of PMD Act (Published in 2019/12/4)

2. Review of the roles of pharmacists and pharmacies so patients can use drugs with peace of mind in familiar communities

i. The requirement for pharmacists to track medication adherence and give instructions as needed in addition to the time of dispensing. The obligation for pharmacists to make efforts in providing information about medication adherence to other health care providers.

ii. Introduction of system for prefectural governor-certified pharmacies with specific function (titles exclusive) so patients can choose pharmacies appropriate to their needs

iii. Provision of online medication instructions such as video calls as an exception to the face-to-face requirement according to certain rules

Outline of the bill for the partial revision of PMD Act (Published in 2019/12/4)

3. Establishment of regulatory compliance systems to gain trust

i. Requiring authorisation holders, etc. to establish regulatory compliance systems (setting up work monitoring systems, clarifying the responsibilities of management and front line supervisors, etc.)

ii. Establishment of a surcharge system for sales of drugs by false/exaggerated advertising

iii. Legislation for the verification system regarding the import of drugs unapproved in Japan (import certificate system) and investigation by narcotics agents

iv. Introduction of permission to import Stimulants' Raw Materials by carrying for medical purposes as in the cases of narcotics for medical use

Outline of the bill for the partial revision of PMD Act (Published in 2019/12/4)

4. Others

i. Establishment of a pharmaceutical evaluation and monitoring committee that evaluates/monitors the status of measures to ensure the safety of medicinal products and prevent the occurrence of health hazards

ii. Easing of restrictions on blood sampling based on the advancement of science and technology

Effective date of the partial revision of PMD Act

- 2020/9/1
  - ✓Pioneering drugs (Legislation for the “SAKIGAKE Designation System, drugs for specific purposes)
  - ✓Conditional Accelerated Approval
  - ✓Medical devices to continuous improvement　etc.
- 2021/8/1
  - ✓PACMP
  - ✓Electronically provide package inserts
- 2022/12/1
  - ✓Bar code labeling

DESIGNATION OF PIONEERING DRUGS

Legislation for the "SAKIGAKE Designation System"

- Legislate the system that designates drugs, medical devices, and regenerative medicine products with clearly different mechanisms of action from those that have been approved in Japan and overseas as "pioneering drugs", etc. It should be clearly articulated by law that designated products are given priority for review.
- Legislate the system that designates drugs that are far from meeting medical needs, such as products without dosage and administration for pediatric use, as "drugs for specific use". It should be clearly articulated by law that designated products are given priority for review.
- Stipulate by law that measures should be taken to secure funds necessary to promote studies and to implement taxation for drugs for specific use (limited to drugs intended for the specific use by a small number of patients) as in the cases of the current orphan drugs.

Concepts of pioneering drugs

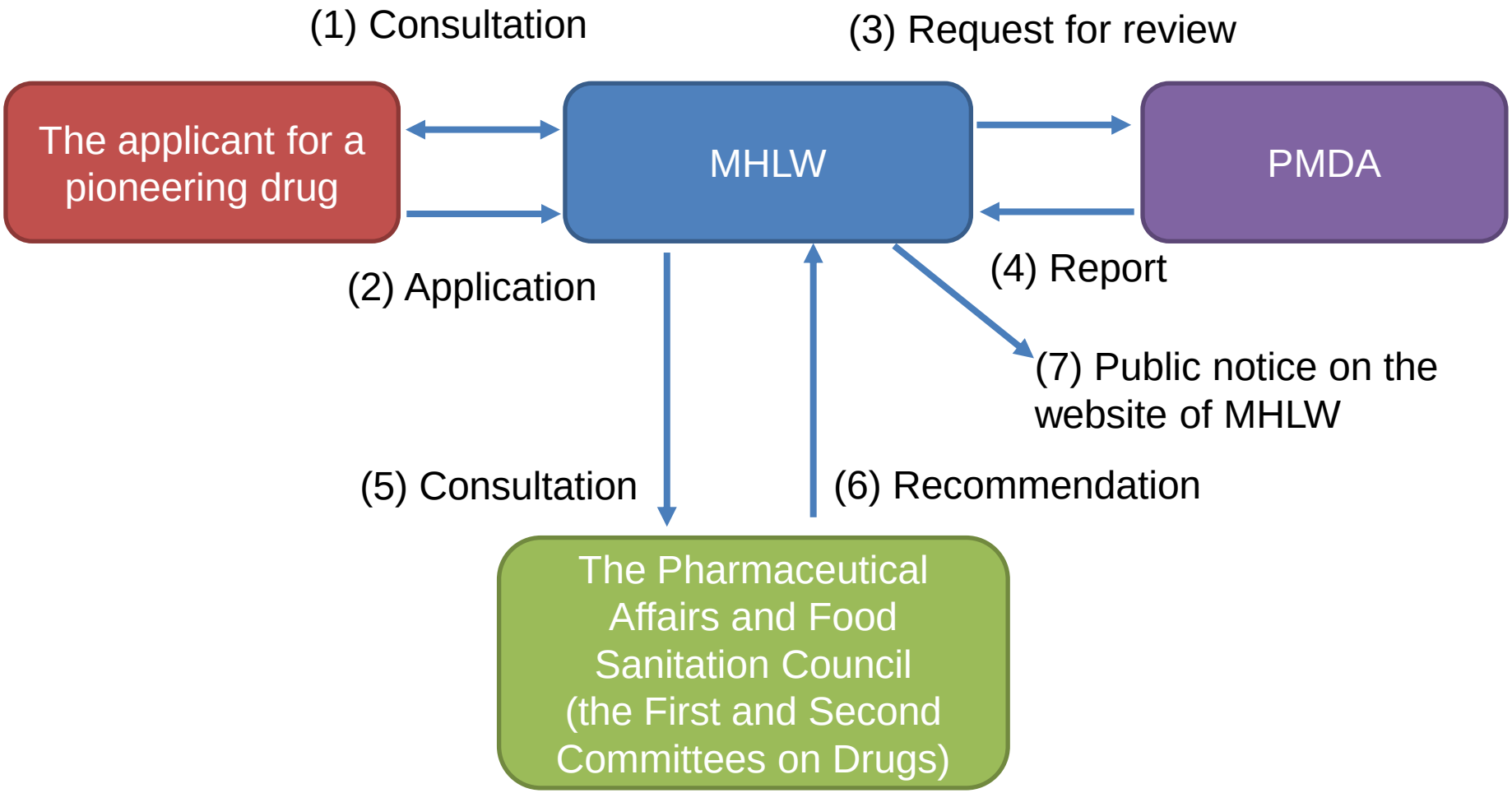
Eligibility for designation

- The Pharmaceutical and Medical Device Act (Article 77, paragraph (2)) defines the following two requirements:
  - Products with clearly different mechanisms of action from those that have been approved in Japan and overseas
  - Products with a particularly excellent value for that purpose

In practice, the same eligibility criteria as for the "SAKIGAKE Designation System" are applied.

- Innovativeness of therapeutic agents
- Seriousness of the diseases to be treated
- Very high efficacy on the diseases to be treated
- Intention to quickly develop and apply in Japan ahead of the world

Procedures to designate pioneering drugs



System for Drugs for specific use

Concept of drugs for specific use

Requirements for designation:

- Significantly unmet medical needs for an intended use,
- Once approved, excellent value is anticipated for such the purposed use .

- The system for drugs for specific use is an approval system focused on unmet medical use (needs)
- Research development and patients' access will be supported in areas with "significant unmet medical needs" outlined by the Ministerial Order.
- The scope includes those that are not suitable for orphan drugs.

➡ First step: Pediatric and AMR

Reference

Discussion on drugs for specific use at sub-committee

Drugs for specific use	**Drugs which have an excellent medical value proposition but need to be developed for indications/dosage and administration different from the previously approved (E.g.) Pediatric dose and administration, change of dosing regimen for prevention of AMR**

Implementation scheme of system for drugs for specific use

- Designation by minister upon council's opinion,
  - Decision based on medical needs.
- Priority review granted,
- Re-examination period for < 6 years,
- If target patients are < 50,000 and the sponsor company has < 1,000 employees, tax incentives and grant support may be applicable.

Concept of potential candidate drugs (for pediatric use, draft)

☑ Applicable	☒ Not applicable
• Addition of dosage and administration for pediatric use for a drug indicated limited number of pediatric patients despite the large number of overall patients. • Dosage form addition especially required for existing products.	• Investigation of pediatric dosage and administration in new drug development. • Drugs subject to orphan drugs (no need for designation for this system).

Drugs subject to the orphan drug provision (such as drugs for pediatric specific diseases) are continued to be applied to the orphan drug system.

Handling of Reexamination period

Category	Period
Orphan drugs	10 y
in case , drugs with a new administration route or new ethical combination drugs	6 y – 8 y
New drugs to evaluate using a pharmacoepidemiologic method	10 y
Drugs containing new active ingredients	8 y
Drugs with a new administration route or new ethical combination drugs	6 y
Drugs for specific use	4 y – 6 y
Drugs with a new indication	
① Pioneering dugs	6 y – 8 y
② In case, existing indication corresponds to orphan drug	5 y 10 m
③ Other cases	4 y
Drugs in new dosage forms new dosage drugs	4 y

OPERATIONS OF CONDITIONAL ACCELERATED APPROVAL

Operations of "Conditional Accelerated Approval" (Pharmaceuticals)

Drugs which are particularly necessary for medical care if the marketing authorization is granted ([i] and [ii]), and for which a clinical study to verify efficacy and safety requiring a large number of subjects is difficult to perform or takes a long time ([iii] and [iv]) (Articles 40 and 45-2 of the Regulation)

[i] Based on the results of a comprehensive assessment with the following criteria, the indications are considered to be serious

1) The disease has a great impact on life (life-threatening)
2) The progression of the disease is irreversible and significantly affects the patient's daily life

"Others" in the notification version is included in 2) as diseases that significantly affect the patient's daily life are expected even though they are not irreversible

[ii] Based on the results of a comprehensive assessment with the following criteria, the drugs are considered to be medically very useful

1) Currently, there are no treatment, prophylaxis, or methods of diagnosis
2) From the viewpoints of efficacy, safety, and physical or mental burden on patients, the medical benefit is superior to available alternatives

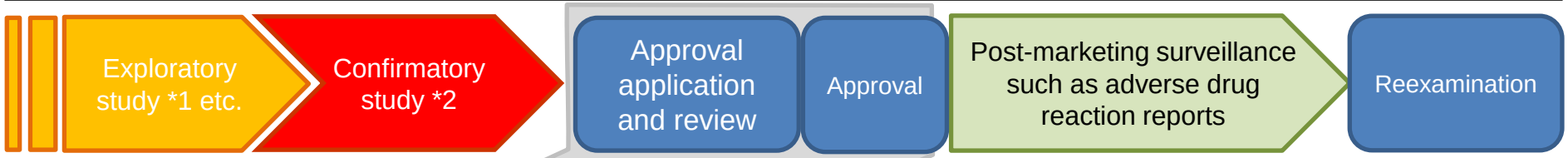
Given priority for review

[iii] It is considered that a confirmatory study is difficult to perform or requires a long time due to the small number of patients, etc.

[iv] It is determined that a certain level of efficacy and safety can be demonstrated in a clinical study, etc. other than a confirmatory study

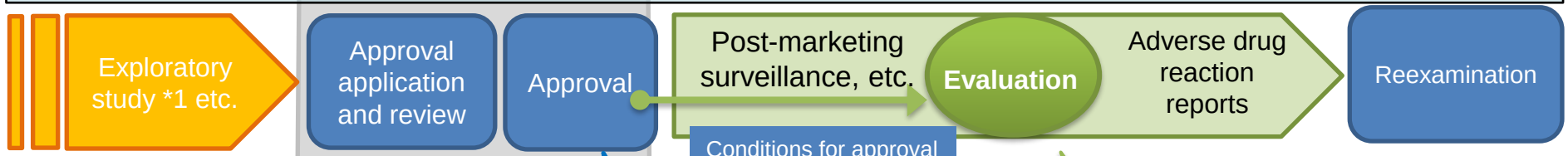
Legislation for the "Conditional Accelerated Approval" (Medicinal products)

Regular approval review



*1 A study to examine the efficacy and safety of the drug and select the dose and regimen by administering a drug to a small number of patients
*2 A study to confirm the efficacy and safety of the drug at the selected dose and regimen by administering a drug to a large number of patients

Conditional accelerated approval



- Demonstrate a certain level of efficacy and safety in clinical studies other than a confirmatory study, for accelerated approval
- Reduce the total approval time through handling as a product designated for priority review

* Real-world data refer to various data collected in actual clinical practice, unlike clinical studies.

Conditions for approval

■ **Make a condition to each product based on the data obtained at the time of approval:**
- **Data collection to reconfirm the post-marketing efficacy and safety**

(including the use of real-world data)
- **Setting requirements for study sites, investigators, etc.**

■ **Evaluate the quality, efficacy, and safety based on the results of post-marketing surveillance during the period of re-examination.**

■ **Change a condition and/or give an order to implement safety measures according to the evaluation results.**

POST-APPROVAL CHANGE MANAGEMENT PROTOCOL (PACMP)

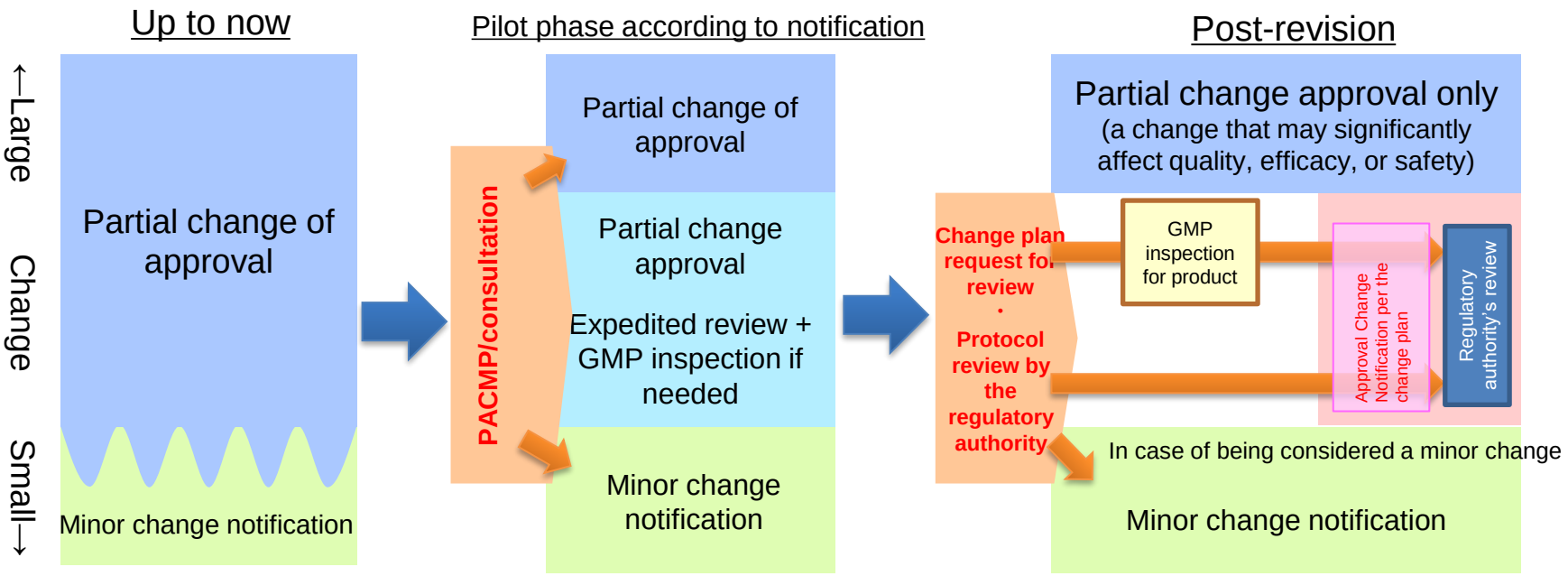
System for Change of Approval Items Based on PACMP

System Overview

1. Market authorization holder and the regulatory authority agree on contents of proposed changes to the manufacturing method and change category in advance.
2. Assessment based on the agreed evaluation methods.
3. Once expected results are obtained, approved items related to quality may be changed to those proposed in a draft in an expedited manner.

Revision of Procedures for Changing Approved Items Related to Quality of Pharmaceuticals

Pilot implementation initiated per Notification since March 2018.



MANAGEMENT OF REGULATORY REVIEW OF DRUGS FOR COVID-19

Management of Regulatory Review of Drugs for COVID-19

- Rapid development of effective therapy for COVID-19 is a pressing matter. On the other hand, our knowledge about the treatment of COVID-19 is still limited.
- Accordingly, to help support rapid commercialization of drugs for this disease, results of publicly supported clinical research conducted in Japan, as well as clinical trials, will be considered during regulatory review.
- Additionally, to improve preparedness of applicant/developer, we will clarify how those data are handled in a regulatory review, based on the characteristics of the data.

Regarding the handling of drugs, etc. for approval examination for COVID-19

(2020/5/12 PSEHB/PED Notification No. 0512-4, PSEHB/MDED Notification No. 0512-1)

1. Top priority is given to medications for COVID-19.
2. Preliminary consultation is available on NDA dossier (data).
3. It is clarified that limited data is accepted (i.e., clinical study report is not needed if a certain level of results obtained by a publicly funded clinical research).
4. Conditions for 3. are as follows: Data conform to a certain standard (GCP), or additional clinical study results are submitted later.
5. Conditions are given at a later date, including the relevant data submission, and the approval may be revisited (or withdrawn) based on the submitted data.

Activities Status Toward Commercialization of COVID-19 Vaccines

- R&D and accelerated regulatory review
- Establishment of production facility
- Procurement of overseas vaccines
- To establish an immunization system logistic support system etc.

Concept of evaluation of COVID-19 vaccine

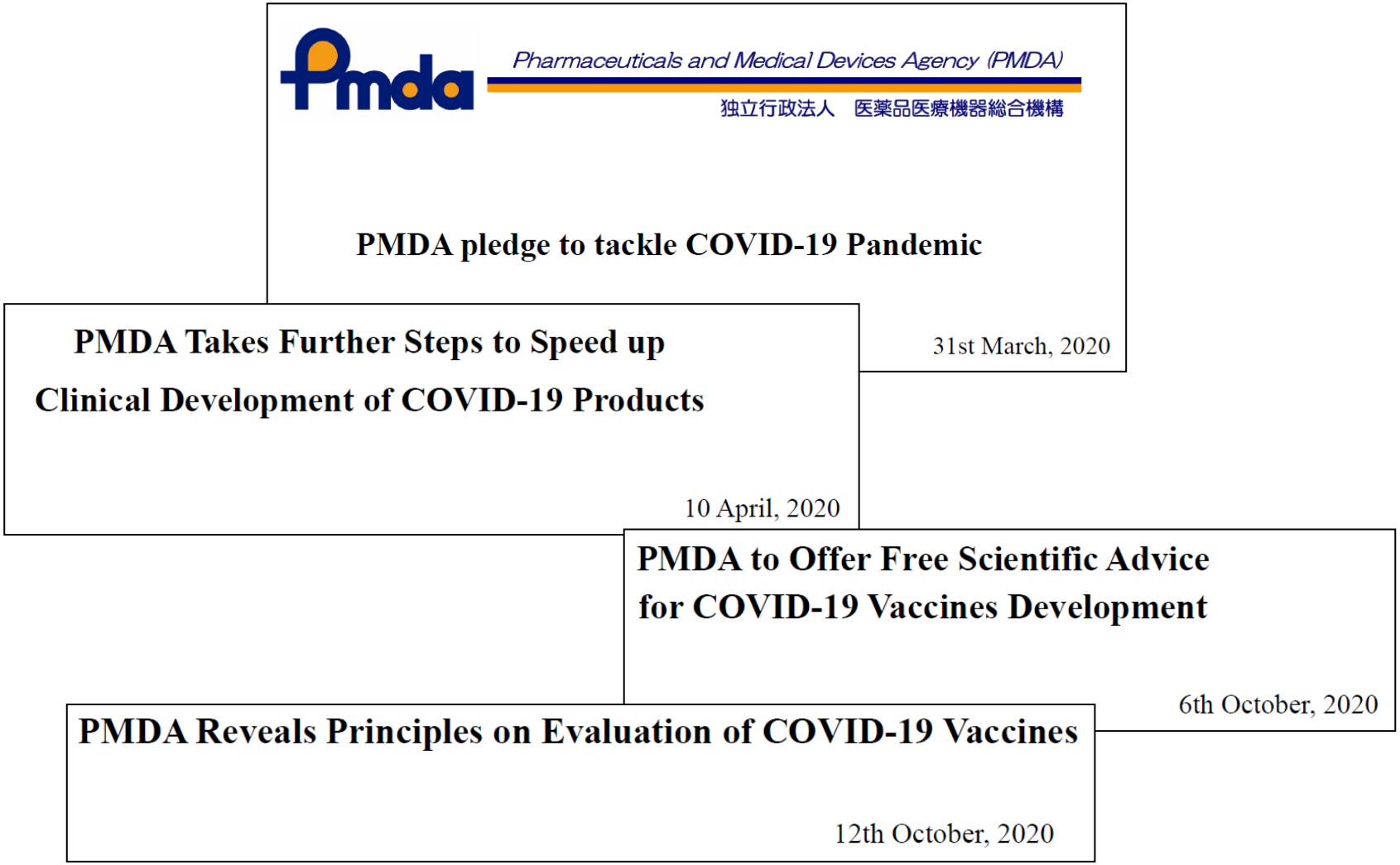
2020/9/2 Office of Vaccines PMDA

It presents the concept of evaluation of efficacy and safety required for the development of CIVID-19 vaccine in Japan.

- Nonclinical: Pharmacology; Safety study; ADME; ADE; Cartagena
- Clinical: Dosage; Immunogenicity; Efficacy; Safety; Study designing; Follow-up; evaluation in elderly, pregnant / lactating women, children
- Correspondence at the time of marketing

https://www.pmda.go.jp/files/000236327.pdf

Management of Regulatory Review of Drugs for COVID-19



Thank you for your attention !