

CMC Strategy Forum Japan 2021
6-8 December, 2021

PMDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

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Outline

1. Outline of the partial revision of PMD Act
 - 1) Post-Approval Change Management Protocol (PACMP)
 - 2) Review of the scope of minor changes to approved matters

2. Management of Regulatory Review of Drugs for COVID-19

1. Outline the partial revision of PMD Act

1) POST-APPROVAL CHANGE MANAGEMENT PROTOCOL (PACMP)

System for Change of Approval Items Based on PACMP

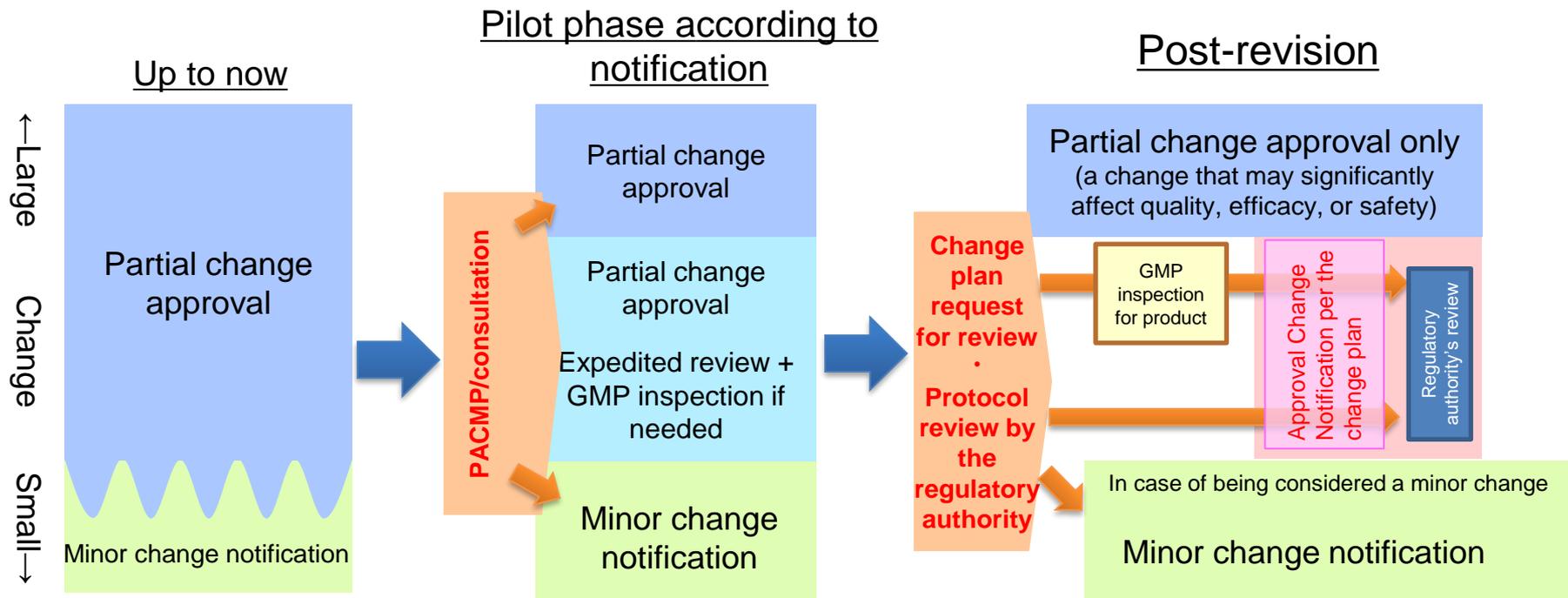
System Overview

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

PACMP has been enforced on August 1, 2021

(Pilot implementation initiated per Notification since March 2018.)



Changes to approved matters for which confirmation of the PACMP can be obtained

1. Changes should be made to the items listed in Article 68-3 of the Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act (hereinafter referred to as the “Ordinance”), such as manufacturing methods, specifications, and testing methods.
2. Changes listed in Article 68-4 of the Ordinance, such as a change to a new manufacturing method where it is difficult to predict the impact on quality if implemented, and an important change in the method of inactivation or removal of pathogenic factors, are ineligible.
3. A pharmaceutical quality system should be properly operated in line with ICH Q10, and manufacturing and quality control should be conducted at the drug manufacturing facility pertaining to the change concerned. The marketing authorization holder, etc. should periodically check the actual operation of the pharmaceutical quality system.
4. For drugs for which a description modification notification has been submitted, changes should be made to drugs for which the underlined parts in the approved matters or the drug master file (hereinafter referred to as “MF”) have been deleted upon completion of the PMDA’s confirmation of the description modification notification based on the post-submission application for partial change approval.

Note: For the time being, changes related to MF registration details will not be covered in this scheme.

All of [1]-[4] must be satisfied

What differs from the pilot phase

1. All drugs and quasi-drugs (plus cosmetics) are covered.
2. Confirmation of PACMPs is not within the scope of the PMDA's consultation service, but is handled upon application to the Minister, etc.
3. For changes for which a prior notification of partial change in manufacturing methods, etc. has been submitted, the change may be implemented unless otherwise indicated by the authority within 40 business days (or 20 business days in special cases) after notification.

1. Outline the partial revision of PMD Act
 - 2) Review of the scope of minor changes to approved matters

Review of the scope of minor changes to approved matters that can be made by notification [1]

- The scope of minor changes to approved matters of drugs, etc. is specified in Article 47 of the Enforcement Regulations of the PMD Act.
 - “Deletion of items listed in specifications and test methods and changes in specifications,” which was listed as being outside the scope of the above, has now been deleted. Accordingly, changes in the specifications and test methods, etc. may also be subject to minor change notification.
- Article 47 of the Enforcement Regulations of the PMD Act (scope of minor changes to approved matters)

Before revision

Minor changes specified by Order of the Ministry of Health, Labour and Welfare prescribed in Article 14, paragraph (9) of the Act are those other than those set forth in each of the following items:

- (i) changes to manufacturing methods, etc. influencing essential qualities, features, or safety of the product;
- (ii) deletion of matters set forth in the specifications and the test methods and changes of the specifications;
- (iii) changes concerning the inactivation or removal method for pathogenic factors;
- (iv) addition, change, or deletion to/of usages, dosages, efficacies, or effects;
- (v) beyond changes set forth in each of the preceding items, those that may influence the quality, efficacy, and safety of the product.

Review of the scope of minor changes to approved matters that can be made by notification [2]

After revision

Minor changes specified by Order of the Ministry of Health, Labour and Welfare prescribed in Article 14, paragraph (9) of the Act are those other than those set forth in each of the following items:

(i) changes to manufacturing methods, etc. influencing essential qualities, features, or safety of the product;

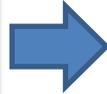
~~(ii) deletion of matters set forth in the specifications and the test methods and changes of the specifications;~~ ← Deleted

(iii) changes concerning the inactivation or removal method for pathogenic factors;

(iv) addition, change, or deletion to/of usages, dosages, efficacies, or effects;

(v) beyond changes set forth in each of the preceding items, those that may influence the quality, efficacy, and safety of the product.

As a result of this revision:



Any deletion or modification of “specifications and test methods” is subject to minor change notification.



Matters that may affect the quality, efficacy, and safety of products as set forth in new Item (iv) are not subject to minor change notification and remain subject to partial change approval.

2. Management of Regulatory Review of Drugs for COVID-19

Handling of COVID-19 drugs, etc. in the approval review process[1]

- ◆ There is a need to accelerate the development of therapeutic drugs, etc. that are effective for COVID-19. However, only a limited amount of knowledge is available about the treatment of COVID-19.
- ◆ In order to promptly bring therapeutic drugs, etc. into practical use, the results of public clinical research conducted in Japan other than clinical trials should also be proactively reflected in the pharmaceutical approval process.
- ◆ To help applicants and developers foresee future developments, the handling of applications in the review and approval process based on data characteristics should also be clarified.

Handling of COVID-19 drugs, etc. in the approval review process[2]

The following notice was issued as a special measure concerning drugs, etc. against COVID-19 (May 12, 2020).

- [1] Drugs, etc. for COVID-19 should be reviewed with the highest priority.
- [2] Prior consultation should be conducted regarding the application dossier (data).
- [3] It is clearly stated that limited data may be acceptable (public clinical research data with a certain level of plausibility may suffice, even without clinical study [trial] data).
- [4] As a condition of [3], the data should be based on certain standards (GCP), or clinical study results should be submitted separately.
- [5] One condition is that data should additionally be submitted after approval, and the approval may be reviewed or even revoked based on such data.

Special approval systems in Japan[1]

System name	Special approval	Conditional early approval
System type	Part of the approval system	Same as on the left.
Supporting law	Article 14-3 of the Pharmaceuticals and Medical Devices Act	Article 14-10 of the Pharmaceuticals and Medical Devices Act
Timing of application	<p>Applicable when [1] to [3] below are satisfied.</p> <p>[1] The proposed drug is necessary to prevent the spread of diseases that may seriously affect the lives and health of the people and other health hazards.</p> <p>[2] There is no appropriate treatment modality other than the use of the proposed drug.</p> <p>[3] The proposed drug is distributed in countries that have a regulatory system of the same level as that in Japan (cabinet order is required).</p>	<p>Applicable if all of the following are satisfied.</p> <p>[1] The proposed drug is indicated for serious diseases (e.g., having a significant impact on life).</p> <p>[2] The medical usefulness of the proposed drug is high since, for example, there are no existing therapies, etc.</p> <p>[3] It is difficult or takes a considerable period of time to conduct confirmatory clinical studies due to a small number of patients, etc.</p> <p>[4] The results of studies other than confirmatory clinical studies have demonstrated a certain level of efficacy and safety.</p>
Authorizer	Minister of Health, Labour and Welfare	Same as on the left.

Special approval systems in Japan[2]

System name	Special approval	Conditional early approval
Safety consideration	As in regular approval, reporting of adverse reactions, etc. are required.	Same as on the left.
Difference from regular approval (exceptions, conditions, etc.)	<ul style="list-style-type: none"> ▪ Exemption from investigations related to quality assurance and reliability, and from authorization of marketing and manufacturing. ▪ Moratorium on the submission of application dossier other than clinical study data and matters to be included in the package insert. ▪ Matters described on the label can be left in English, provided that Japanese text is included in the package insert, etc. ▪ The Minister of Health, Labour and Welfare may revoke approval when the applicable conditions are no longer satisfied. 	<ul style="list-style-type: none"> ▪ Approval applications may be filed without attaching the results of confirmatory clinical studies. ▪ Conditions for collecting information on efficacy and safety are imposed at the time of approval. ▪ After approval, evaluation of the information collected based on the above conditions should be carried out within the period specified by the Minister of Health, Labour and Welfare, and the conditions should be changed accordingly.
Past case	<ul style="list-style-type: none"> ▪ New influenza vaccine (2010) ▪ Remdesivir (May 7, 2020) ▪ COVID-19 vaccine (Pfizer) (February 14, 2021) 	<p>Implemented on September 1, 2020 (The “conditional early approval” as specified in the previous notification was applied to new drug approval for lorlatinib, an additional indication of Keytruda, etc.)</p>

Drugs that are or could be used for the treatment of COVID-19 [1]

1. Drugs approved for use in the treatment of COVID-19

As of Nov 5, 2021

1-1. Veklury (remdesivir) (marketing authorization holder: Gilead Sciences, Inc.)

- An RNA polymerase inhibitor developed (as an infusion) to treat Ebola hemorrhagic fever.
- Granted a special approval on May 7, 2020.

Special approval granted on May 7, 2020

1-2. Decadron (dexamethasone) (marketing authorization holder: Nichi-Iko Pharmaceutical Co., Ltd.), etc.

- A steroid drug approved in Japan for the treatment of severe infections and interstitial pneumonia.
- It was listed as a standard treatment (drug approved in Japan) in the Guide to the Treatment of COVID-19, Version 2.2.

1-3. Olumiant (baricitinib) (marketing authorization holder: Eli Lilly Japan K.K.)

- A Janus Kinase (JAK) inhibitor (oral drug) approved in Japan for the treatment of rheumatoid arthritis, etc.
- Approved for concomitant use with remdesivir on April 23, 2021.

Approval granted on April 23, 2021

Drugs that are or could be used for the treatment of COVID-19 [2]

1-4. Ronapreve (casirivimab/Imdevimab) (marketing authorization holder: Chugai Pharmaceutical, Co., Ltd.)

- A neutralizing antibody drug (drip infusion/ subcutaneous injection) that binds to the spike protein of the novel coronavirus.
- This drug was granted a special approval on July 19, 2021.

Special approval granted on July 19, 2021

1-5. XEVUDY (Sotrovimab) (marketing authorization holder: GlaxoSmithKline K.K.)

- A neutralizing antibody drug (drip infusion) that binds to the spike protein of the novel coronavirus.
- This drug was granted a special approval on September 27, 2021.

Special approval granted on Sep 27, 2021

Drugs that are or could be used for the treatment of COVID-19 [3]

2. Another drug used in the treatment of COVID-19

2-1. Heparin

- Patients with COVID-19 are at risk for thrombosis due to cytokine storm and vascular endothelial damage. Obstruction of alveolar capillaries and other conditions have been demonstrated in autopsy cases. (Severe infection and respiratory failure are moderate risk factors for deep vein thrombosis.)

3. Drug for which approval application has been filed

Approval
application filed on
October 16, 2020

3-1. Avigan (favipiravir) (marketing authorization holder: FUJIFILM Toyama Chemical Co., Ltd.)

- An RNA polymerase inhibitor (oral drug) that has been approved in Japan for novel or re-emerging influenza.
- Although stockpiled by the government, this drug is not marketed because of its teratogenicity.

(The remaining parts are intentionally omitted)

Position of each therapeutic drug in the treatment of COVID-19

Figure 4-1. Summary of severity-based management

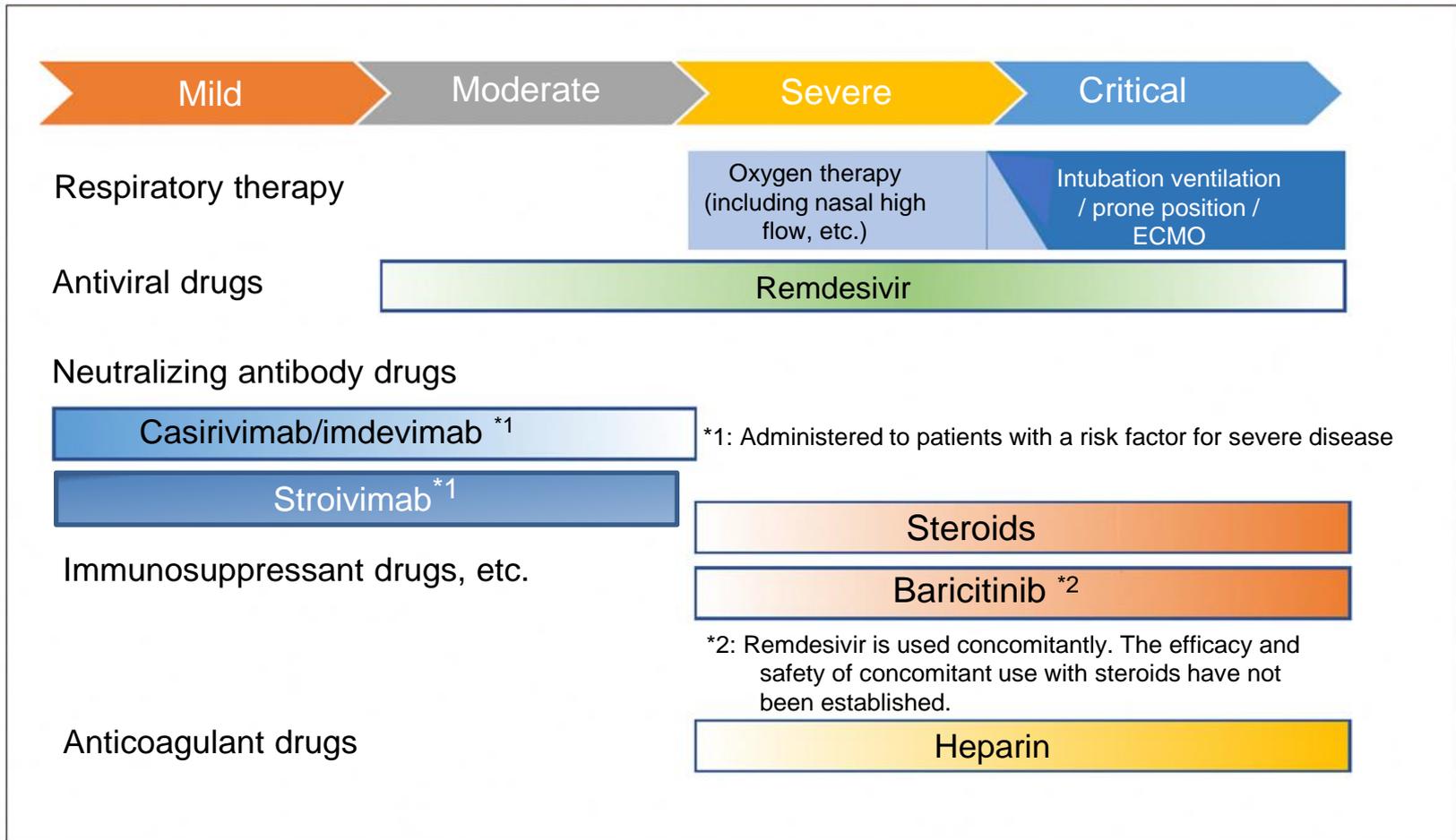


Figure excerpted from the Guide to the Treatment of COVID-19, Version 5.2, with some revisions.

Approach in the evaluation of COVID-19 vaccines [1]

- The concept was formulated by the PMDA in consultation with experts, taking into account discussions by the International Coalition of Medicines Regulatory Authorities (ICMRA, an international collaboration of regulatory authorities in Europe, the US, Japan, and other countries) and guidance from the US FDA (released on September 2, 2020).

Key points

Efficacy evaluation :

- In principle, clinical trials should be conducted with the primary endpoint of disease prevention. The secondary endpoints should include endpoints related to severity.
- Confirmation of an immunogenicity index related to the prophylactic effect may allow for efficacy evaluation.

Approach in the evaluation of COVID-19 vaccines [2]

Key points

Evaluation in Japanese clinical studies:

- In view of the differences in prevalence, viral strains, and ethnic factors among countries and regions, it is necessary to conduct Japanese clinical trials to examine the efficacy and safety in Japanese subjects.

Efficacy evaluation of foreign candidate vaccines:

- If a large-scale confirmatory clinical study is conducted overseas with the primary endpoint being the prevention of disease onset, it may be sufficient to conduct a Japanese clinical study involving Japanese subjects to establish the immunogenicity (antibody titer, etc.) and safety profiles in Japanese patients.

Approach in the evaluation of COVID-19 vaccines [3]

Key points

Safety evaluation:

- Specific local reactions (e.g., swelling, redness, induration, and pain) and specific systemic reactions (e.g., fever, headache, malaise, and myalgia) observed within at least 7 days following vaccination, and adverse events observed within at least 28 days following vaccination should be collected. Depending on the characteristics, etc. of the candidate vaccine, a longer period may be appropriate.

Follow-up during clinical trials:

- A follow-up period of at least 1 year should be planned in clinical studies in order to collect information on long-term efficacy and safety after vaccination. Information on persistence, etc. of antibody titers and on adverse events, including risk assessment for disease enhancement, should be collected.

Key points

Disease enhancement (antibody-dependent enhancement [ADE]):

- It is necessary to evaluate the immune (Th1/Th2) balance, etc. examined in non-clinical pharmacology studies prior to clinical studies and to estimate the risk of disease enhancement.
- New findings should be evaluated using new methods as appropriate.

Pharmacokinetic studies:

- For mRNA vaccines, DNA vaccines, and recombinant virus vaccines, evaluation of post-dose biodistribution is required.

Approach in regulatory evaluation of vaccines for variants (Addendum 1) [1]

As for the COVID-19 vaccines, it is expected that the development of vaccines for variants, which are partially modified versions of the currently used vaccines (original vaccines), will advance in the future. Accordingly, the approach in evaluation of vaccines for variants was organized in consideration of international consistency and was released in April 2021 as Addendum 1 to the “Approach in the Evaluation of COVID-19 (SARS-CoV-2) Vaccines” issued in September 2020.

Key points

- The modified vaccines for variants covered in the document are as follows:
 - ❖ Vaccines derived from an existing COVID-19 vaccine that has already been approved in Japan (original vaccine)
 - ❖ Vaccines developed by the same developer/manufacturer for the purpose of obtaining protection against variants
 - ❖ Vaccines produced by using the same or very similar manufacturing and control methods as the original vaccine

Approach in regulatory evaluation of vaccines for variants (Addendum 1) [2]

Key points

- Evaluation may be performed by mainly confirming the items shown below, based on data focusing on the differences between the original vaccine and the vaccine for variants. In that case, it is not necessary to conduct a new large-scale clinical study to verify the prophylactic effect.
- ❖ Comparability and consistency of manufacturing methods and quality specifications
- ❖ Comparability of the immunogenicity (neutralizing antibody titer) between the vaccine for variants (against a variant strain) and the original vaccine (against the original strain).

Approach in regulatory evaluation of vaccines for variants (Addendum 1) [3]

Key points

- In principle, it is not necessary to conduct a new Japanese clinical trial of a vaccine for variants in the following cases.
 - ❖ The comparability of the original vaccine has been demonstrated between Japan and overseas in terms of immunogenicity, AND
 - ❖ The comparability in terms of immunogenicity (neutralizing antibody titer) has been demonstrated overseas between the vaccine for variants (against a variant strain) and the original vaccine (against the original strain).

Covid-19 vaccines approved in Japan[1]

Product name	Comirnaty Intramuscular Injection	COVID-19 Vaccine Moderna Intramuscular Injection	Vaxzevria Intramuscular Injection
Type	mRNA vaccine	mRNA vaccine	Virus vector vaccine
Marketing authorization holder	Pfizer Japan Inc.	Takeda Pharmaceutical Company Co., Ltd.	AstraZeneca K.K.
Date of approval application	December 18, 2020	March 5, 2021	February 5, 2021
Date of regulatory approval (special approval)	February 14, 2021	May 21, 2021	May 21, 2021
No. of vaccinations, etc.	<ul style="list-style-type: none"> • 2 (3 weeks apart, intramuscular injection) • Indicated for ages from: 12 years 	<ul style="list-style-type: none"> • 2 (4 weeks apart, intramuscular injection) • Indicated for ages from: 18 years 	<ul style="list-style-type: none"> • 2 (4 to 12 weeks apart, intramuscular injection) • Indicated for ages from: 18 years
Storage condition	-90 °C to -60 °C for 6 months following manufacture 14 days following transfer to an environment at -25 °C to -15 °C 2 °C to 8 °C for 1 month following thawing	-25 °C to -15 °C for 6 months following manufacture	2 °C to 8 °C for 6 months following manufacture
Major safety issues	Anaphylaxis	Swelling at the vaccination site	Extremely rare thrombosis



Covid-19 vaccines approved in Japan[2]

Product name		Comirnaty Intramuscular Injection	COVID-19 Vaccine Moderna Intramuscular Injection	Vaxzevria Intramuscular Injection
Clinical study result	Foreign phase III studies	Prophylactic effect: 95.0%	Prophylactic effect: 94.1%	Prophylactic effect: Approx. 70% (pooled analysis)
	Japanese phase I/II studies	Immunogenicity (increase in antibody titer) comparable to or higher than that in foreign clinical studies was demonstrated.	Immunogenicity (increase in antibody titer) comparable to or higher than that in foreign clinical studies was demonstrated.	Immunogenicity (increase in antibody titer) comparable to or higher than that in foreign clinical studies was demonstrated.
	Adverse events observed	Pain at the vaccination site (> 80%) / Fatigue (> 60%) / Headache (> 50%) / Myalgia (> 30%) / Chills (> 30%) / Arthralgia (> 20%) / Diarrhea, fever, and swelling at the vaccination site (> 10%)	Pain at the vaccination site (> 80%) / Fatigue (> 60%) / Headache (> 50%) / Myalgia (> 50%) / Chills (> 10%) / Arthralgia (> 40%) / Diarrhea, fever, and swelling at the vaccination site (> 10%)	Pain at the vaccination site (> 50%) / Tenderness (> 50%) / Fatigue (> 40%) / Malaise (> 40%) / Headache (> 40%) / Myalgia (> 40%) / Chills (> 30%) / Arthralgia (> 20%) / Nausea (> 20%) / Feeling hot, pruritus, and contusion (> 10%)
Major safety issues		Anaphylaxis	Swelling at the vaccination site	Extremely rare thrombosis

Review of the regulatory approval process for the approval of domestically produced vaccines

Temporary measures

- ❖ With regard to evaluation of the efficacy of COVID-19 vaccines, it has been necessary to conduct placebo-controlled studies (on a scale of tens of thousands of subjects) to verify the efficacy in preventing the onset of symptoms based on the international consensus reached through discussions at the International Coalition of Medicines Regulatory Authorities (ICMRA). As the use of preceding vaccines has progressed, however, it has become difficult to conduct placebo-controlled studies for new vaccines, and this has become a common global issue.
- ❖ Since it is important to solve this issue from the perspective of the development of domestically produced vaccines, Japan will take the lead in initiating discussions at the ICMRA on the design of confirmatory studies as an alternative to placebo-controlled studies. We will aim to reach consensus as soon as possible.
- ❖ Based on discussions at the ICMRA, the government will provide strong support, along with the prescribed budgetary measures, to help anticipate the eventual consensus before it is reached so that Japanese companies can promptly initiate and complete confirmatory studies.

Review of the regulatory approval process for the approval of domestically produced vaccines

Medium- and long-term measures

- ◆ In order to facilitate clinical studies of therapeutic drugs and vaccines in the event of an emergence of a new infectious disease, a protocol (draft) on the framework of government-led clinical studies in emergencies will be prepared in advance in line with international consensus, and will be compiled together with points requiring attention for the conduct of such studies.
- ◆ In quickly presenting the concept behind scientific evaluation necessary in emergency situations, it is necessary to always develop evaluation methods and issue guidelines (guidance) on various technologies, including the latest technical modalities. To this end, departments and systems will be set up.
- ◆ Once the COVID-19 pandemic becomes under control, how the system (requirements, standards, compensation, exemption, etc.) should be for allowing special use in emergency situations will be examined with reference to the current measures taken by other countries, in the context of government-wide discussion on how to deal with emergencies after review of the current measures.

Progress in COVID-19 vaccine development (in Japan) [selected]

	Basic information	Status of efforts	Outlook for the production system
[1] Shionogi & Co. National Institute of Infectious Diseases / UMN Pharma Recombinant protein vaccine	A protein (antigen) of the virus is created by genetic recombination technology and administered to humans.	Phase I/II studies were started (December 2020).	Build a system capable of producing vaccines for 30 million people by the end of 2021. 22.3 billion yen in subsidies given as part of the urgent production system improvement project.
[2] Daiichi Sankyo The Institute of Medical Science, The University of Tokyo mRNA vaccine	Viral mRNA is administered to humans. Virus proteins (antigens) are synthesized in the human body.	Phase I/II studies were started (March 2021).	6.03 billion yen in subsidies given as part of the urgent production system improvement project.
[3] AnGes Osaka University / Takara Bio DNA vaccine	DNA of the virus is administered to humans. Virus proteins (antigens) are synthesized in the human body from DNA via mRNA.	Phase I/II studies were started. Phase II/III studies were started.	Takara Bio, AGC, Kaneka, etc., will undertake the production. 9.38 billion yen in subsidies given as part of the urgent production system improvement project.
[4] KM Biologics The Institute of Medical Science, The University of Tokyo/NIID/NIBI Inactivated vaccine	An inactivated virus is administered to humans (conventional vaccine).	Phase I/II studies were started (March 2021).	6.09 billion yen in subsidies given as part of the urgent production system improvement project.

Thank you for your attention