Provisional Translation (as of April 2026) *

Administrative Notice
February 6, 2026

To: (separately addressed)

Pharmaceuticals and Medical Devices Agency
Office of Vaccines and Blood Products

Considerations on Utilization of the Platform-based Approach in Non-Clinical Safety Evaluation of mRNA-LNP Vaccines for Prevention of Infections (Early Consideration)

The Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") deeply appreciates your understanding of and cooperation in our review activities.

In Japan, non-clinical safety of vaccines for prevention of infections has been evaluated according to characteristics of individual vaccine products with reference to the "Revision of the 'Guideline for Non-Clinical Studies of Vaccines for Prevention of Infections'" (PSB/PED Notification No. 0327-1, dated March 27, 2024), etc.

On the other hand, keeping animal studies to the minimum extent scientifically justified is considered as one of the important issues from the viewpoints of following a global trend toward reduction of animal studies and promoting rapid development of safe and effective vaccines for prevention of infections.

PMDA has organized the concept for utilization of platform-based approach in non-clinical safety evaluation of mRNA-LNP vaccines for prevention of infections and inform you of these views as provided in the appendix.

Please note that "Early Consideration" is a reference for promoting the practical application of new technologies and the development of innovative pharmaceuticals, even though scientific knowledge and information have not necessarily been sufficiently accumulated at this stage, and that it may change in the future due to newly obtained knowledge and scientific progress and other related scientific developments.

(addressed to)
Federation of Pharmaceutical Manufacturers' Associations of Japan
Japan Pharmaceutical Manufacturers Association
Japan-Based Executive Committee, Pharmaceutical Research and Manufacturers of America
European Federation of Pharmaceutical Industries and Associations
Japan Association of Vaccine Industries
Japan Blood Products Association

Early Consideration on Utilization of the Platform-based Approach in Non-Clinical Safety Evaluation of mRNA-LNP Vaccines for Prevention of Infections

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1. Background

On January 30, 2020, the World Health Organization (hereinafter referred to as "WHO") declared that the outbreak of diseases caused by novel coronavirus (hereinafter referred to as "SARS-CoV-2") infection (hereinafter referred to as "COVID-19") fulfilled the criteria for a Public Health Emergency of International Concern (hereinafter referred to as "PHEIC").[1)] In December 2020, when vaccines against COVID-19 were being developed across the world, the world's first mRNA-LNP vaccines[note 1)] were granted an Emergency Use Authorization in the US. Since then, a mRNA-LNP platform manufacturing[note 2)] has been applied to development of vaccines against various infections across the world including Japan.

Even after WHO announced that COVID-19 no longer constituted a PHEIC, new SARS-CoV-2 variants with altered infectivity have emerged and repeatedly caused epidemic waves. Under such circumstances, effective SARS-CoV-2 vaccines against prevalent strains are in solid social demand. In addition, from the viewpoint of public health, a significance can also be found in the promotion of development of vaccines for prevention of infections to prepare for potential outbreaks of respiratory infections with influenza viruses and RS viruses and imported infections with Zika virus and *Plasmodium*.

In development of a vaccine for prevention of infections, a concept of utilizing information from other vaccine products based on the same platform for non-clinical safety evaluation or a platform-based approach (hereinafter referred to as "PFA") was initially proposed at the "Global regulatory workshop on COVID-19 vaccine development" held under the International Coalition of Medicines Regulatory Authorities (ICMRA)[2)] on March 18, 2020 and then reflected in a WHO document[3)] issued in 2022.

In Japan, the "Revision of the 'Guideline for Non-Clinical Studies of Vaccines for Prevention of Infections'" (PSB/PED Notification No. 0327-1, dated March 27, 2024) has been deemed a reference guideline for non-clinical safety evaluation of vaccines for prevention of infections, but the guideline does not reflect experiences with the commercialization and approval review of mRNA-LNP vaccines to date. Practically, the non-clinical safety evaluation necessary for the start

note 1) Vaccines for prevention of infections comprised of lipid nanoparticles (LNPs) encapsulating mRNA coding antigen proteins derived from exogenous organisms such as viruses
note 2) Strategic methodology for the development of new drugs, etc. produced through similar processes by the same applicant. For definitions in this document, see Section 2 Glossary and scope.

of clinical studies including a First-in-Human (FIH) study and applications for marketing approval has been performed according to the characteristics of individual vaccine products with reference to not only the above guideline but also WHO guidelines and other relevant international guidelines.[3)4)5)]

This document presents PMDA's views on PFA utilization in non-clinical safety evaluation of mRNA-LNP vaccines to facilitate effective development of vaccines for prevention of infections while ensuring that safety in humans is set as an essential prerequisite from the viewpoints of these backgrounds and the current global trend toward reduction of animal studies.

Please note that the views presented in this document are subject to change based on new knowledge that may become available in future.

2. Glossary and scope

- Glossary
  - Platform manufacturing

    A strategic methodology for the development of new drugs, etc. produced through similar processes to those previously used for production of other drugs in the same type by the same applicant. The platform manufacturing in this document is described for the case where a new mRNA-LNP vaccine is produced utilizing steps for in vitro transcription, purification, and LNP encapsulation that have been established for approved vaccines.
  - Platform-based approach (PFA)

    The PFA in this document refers to a strategy applied to development of a new mRNA-LNP vaccine utilizing the documented platform production with at least 1 approved vaccine product in Japan and intended to utilize the non-clinical safety study results from the approved mRNA-LNP vaccines produced on the same platform as data supporting start of clinical studies in Japan.
  - On-target toxicity

    On-target toxicity refers to toxicity occurring in vaccine recipients attributable to excessive immune response (humoral or cellular immunity) to the antigen proteins expressed by the active substance (mRNA) of the vaccine.
  - Off-target toxicity

    Off-target toxicity refers to toxicity occurring in vaccine recipients caused by constitutive ingredients of the vaccine except for on-target toxicity (e.g., toxicity of LNPs and impurities, unintended toxicity occurring in vaccine recipients attributable to the antigen proteins expressed by the active substances [mRNA] of the vaccine).

- Scope of application

  The considerations in this document can be applied to vaccines that meet all the conditions below. They may apply to vaccines with similar formulation, specifications, or impurity profile, and applicability will be determined on a case-by-case basis.

  - A new mRNA-LNP vaccine for prevention of infections that is developed by a manufacturer of existing mRNA-LNP vaccines for prevention of infections approved for marketing in Japan and is to be produced on the same platform as that used for the approved vaccines.
  - New mRNA-LNP vaccine of which the platform manufacturing has the quality target product profile (QTPP) in place and critical quality attributes (CQAs) identified and thereby its robustness assured.
  - New mRNA-LNP vaccine using the same formulation (e.g., LNP composition, RNA content, type of modified nucleic acids) as that for the approved vaccines in principle.
  - New mRNA-LNP vaccine of which the final product has the same specifications as those for the approved vaccine products except for altered base sequence of the mRNA active substances and consequently altered quality attributes in principle.
  - New mRNA-LNP vaccine that has an impurity profile equivalent to or less significant than those of the approved vaccines both qualitatively and quantitatively in principle. In addition, except for impurities associated with altered base sequence of the mRNA active substances, new impurities that were not found in the approved vaccines should not be expected.

3. Considerations on PFA utilization in non-clinical safety evaluation

Basic considerations on PFA utilization in non-clinical safety evaluation of new mRNA-LNP vaccines are outlined below. If non-clinical safety study results of approved mRNA-LNP vaccines are used as data supporting the start of clinical trials of a new mRNA-LNP vaccine, firstly the concerned new vaccine should be confirmed to meet the conditions provided under Scope of application in Section 2; and then the non-clinical safety evaluation should be justified with reference to the basic considerations provided below at the time of initial clinical trial notification.

If non-clinical safety study results of approved mRNA-LNP vaccines are used as data supporting an application for marketing approval of a new mRNA-LNP vaccine, the concerned new vaccine should be confirmed to meet the conditions provided under Scope of application in Section 2; and adequacy of the non-clinical safety evaluation of the concerned new vaccine should be explained in view of safety information in clinical studies and scientific knowledge at the time of the application for marketing approval.

<Basic considerations>

- Non-clinical safety evaluation of LNPs

  If both new and approved mRNA-LNP vaccines use LNPs in the same composition (LNPs comprised of the same types of lipid components at the same ratio), toxicity study results of the approved mRNA-LNP vaccines can be used in safety evaluation of the LNPs used in the new mRNA-LNP vaccine from the viewpoint of off-target toxicity evaluation. However, if the proposed dosage regimen (usually presented as a dose of the mRNA active substance) of the new mRNA-LNP vaccine in practical settings exceeds that of the approved vaccines, doses and dosing frequencies used in toxicity studies of the approved vaccines should be confirmed to be equal to or greater than those of the new mRNA-LNP vaccine in practical settings.

- Non-clinical safety evaluation of active substances (mRNA)

  On the assumption that both new and approved mRNA-LNP vaccines use the active substances (mRNA) made of the same types of nucleic acids (for example, both containing the same modified nucleic acids and/or non-modified nucleic acids only), toxicity study results of the approved mRNA-LNP vaccines can be used in safety evaluation of the active substances (mRNA) (including biological degradation products or nucleic acids derived from the mRNA) of the new mRNA-LNP vaccine from the viewpoint of off-target toxicity evaluation. Points to note for the dosage regimens in practical settings are as provided in the above section for non-clinical safety evaluation of LNPs.

- Non-clinical safety evaluation of antigen proteins coded by active substances (mRNA)

  Because the antigen proteins coded by the active substances (mRNA) are supposed to differ between approved and new mRNA-LNP vaccines, toxicity study results of approved mRNA-LNP vaccines cannot be used in safety evaluation of the antigen proteins coded by the active substances (mRNA) of the new mRNA-LNP vaccine. 1) mRNA-LNP vaccines for prevention of infections are designed to induce immune response in vaccine recipients through the following mechanism: after vaccination, the active substances (mRNA) are incorporated into cells where they are translated and expressed; the expressed exogenous antigen proteins are recognized by the recipients' immune system. The extent of immune response induced may differ between approved and new mRNA-LNP vaccines from the viewpoint of the on-target toxicity. 2) Animal studies have limitations in detecting off-target toxicity attributable to the exogenous antigen proteins (for example, unintended toxicity occurring in vaccine recipients such as reactions to the exogenous antigen proteins in human tissues and organs). With the above limitations taken into account and in view of the following points, the safety of the antigen proteins expressed in recipients of the new mRNA-LNP vaccine should be evaluated.

Of note, there are cases where conduct of non-clinical safety studies of the new mRNA-LNP vaccine needs to be considered individually, for example, because of lack of adequate epidemiologic information on the infection to be prevented.

- From the viewpoint of on-target toxicity evaluation, safety concerns associated with immune response to the new mRNA-LNP vaccine should be ruled out by prediction based on non-clinical pharmacology study results of the concerned vaccine.
- From the viewpoint of off-target toxicity evaluation, epidemiologic information on the infection to be prevented by the new mRNA-LNP vaccine (such as information about immune-mediated reactions after the concerned infection in humans, etc.) should be collected and reviewed.

- Non-clinical safety evaluation of impurities in vaccine products

  On the assumption that the new mRNA-LNP vaccine meets the conditions provided under the Scope of application in Section 2, toxicity study results of the approved mRNA-LNP vaccines can be used in safety evaluation of impurities in the new mRNA-LNP vaccine from the viewpoint of off-target toxicity evaluation. Points to note for the dosage regimens in practical settings are as provided in the above sections for non-clinical safety evaluation of LNPs and active substances (mRNA).

In the following cases, applicability of the above considerations for PFA should be determined on a case-by-case basis: where quality attributes of the LNPs, active substances, or impurity profile are different from those of the approved vaccines; and where specifications are changed. If the considerations are applied to such cases, the difference or change should be explained to rule out resultant potential safety concerns in humans.

4. References

1) https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)
2) https://www.icmra.info/drupal/news/March2020/summary
3) Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations. In: WHO Expert Committee on Biological Standardization: seventy-fourth report. Geneva: World Health Organization; 2022: Annex 3(WHO Technical Report Series, No.1039)
4) WHO guidelines on nonclinical evaluation of vaccines. In: WHO Expert Committee on Biological Standardization: fifty-fourth report. Geneva: World Health Organization; 2005: Annex 1(WHO Technical Report Series, No.927)
5) Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. In: WHO Expert Committee on Biological Standardization: sixty-fourth report. Geneva: World Health Organization; 2014: Annex 2(WHO Technical Report Series, No.987)

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