



Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
(b) (6)

ADDENDUM TO PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

From: [REDACTED] CBER, FDA

To: [REDACTED]
Office of Vaccines Research and Review (OVRR), CBER

Through: [REDACTED], CBER, FDA

Subject: Addendum to Pharmacovigilance Plan Review Memorandum

Product: MFLUSIVA (Influenza Virus [(Hemagglutinin; A/H1, A/H3, B/Victorialineage) Vaccine in Lipid Nanoparticles (SM-102, Cholesterol, DSPC, PEG2000-DMG), mRNA-1010)

Sponsor: ModernaTX, Inc.

Application Type /Number: BLA 125869/0

Proposed indication: Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine and is intended for use in persons 50 years of age and older.

Submission Date: December 5, 2025

Action Due Date: August 5, 2026

1 OBJECTIVE

The purpose of this memorandum is to addend the original pharmacovigilance plan (PVP) review memorandum for MFLUSIVA (BLA 125869/0) dated June 28, 2026, to document: 1) CBER's request sent to Moderna asking to revise their MFLUSIVA Accelerated Approval PMR study protocol to include active surveillance of safety events of interest and 2) the review of the proposed safety PMC study synopsis (MFLUSIVA mRNA-1010-P901, fv1.0, July 24, 2026).

2 BACKGROUND

Following the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on June 18, 2026, FDA continued evaluating the submission, considering comments and questions raised at the meeting. On July 10, 2026, OVRP sent Moderna IR #72, asking them to revise their planned Phase 4 effectiveness study to include safety-related outcomes of interest, including deaths, myocarditis/pericarditis, and Guillain-Barre syndrome (GBS).

On July 17, 2026, Moderna responded (IND 27460, Sequence No. 0144) and agreed to conduct an active surveillance study leveraging safety data from the same study cohort as the PMR study (mRNA-1010-P910), but with a distinct protocol with separate objectives, analyses, milestones, and reporting timelines.

On July 22, 2026, FDA sent Moderna IR #78, to request a study synopsis and clarify study details including study population and milestone dates. On July 24, 2026, Moderna responded (BLA 125869, Sequence No. 0106) and acknowledged the Agency's request to expand active safety surveillance for death, myocarditis/pericarditis, and GBS to the indicated population aged 50 years and older as a postmarketing commitment (PMC) and provided the study synopsis of the PMC study *Post-Authorization Active Surveillance Safety Study Using Secondary Healthcare Data to Monitor Real-World Safety of MFLUSIVA (mRNA-1010) Vaccine for the Prevention of Influenza Disease in the United States (fv1.0, July 24, 2026)*.

Although no safety concerns were identified during the clinical development program, a postmarketing active surveillance study was proposed to further evaluate specific safety topics of interest following MFLUSIVA, including death, myocarditis/pericarditis, and GBS.

Numerical imbalances in deaths of unspecified cause were assessed as unlikely to be vaccine related. However, the residual uncertainty will be addressed by the Applicant in their proposed PMC study.

3 REVIEW OF THE mRNA-1010-P901 PMC STUDY SYNOPSIS

3.1 Study design

The proposed PMC study, mRNA-1010-P901, is a retrospective cohort study to actively

monitor prespecified safety topics of interest following the administration of MFLUSIVA in US adults aged ≥ 50 years using secondary healthcare data.

The study includes two stages:

Stage 1 will describe the utilization of MFLUSIVA

Stage 2 will be initiated upon accrual of a sufficient number of MFLUSIVA recipients and outcome events to support the planned analyses, or earlier if initiation is deemed necessary by the Agency.

This stage will inferentially assess the risk of prespecified safety topics of interest after immunization of MFLUSIVA in the included data source(s). Stage 2 will use two distinct study designs to address the reported limitations of secondary healthcare data and answer the relevant safety questions:

- an SCRI design to evaluate GBS and myocarditis/pericarditis/myopericarditis
- an active comparator cohort design to evaluate all-cause mortality. Eligible MFLUSIVA recipients will be sequentially matched to recipients of other licensed influenza vaccines based on calendar date, age group and receipt of concomitantly administered vaccine type.

The required sample size and event thresholds will be specified in the study protocol.

3.2. Primary Objectives

- Describe the uptake of the MFLUSIVA vaccine, characterize MFLUSIVA vaccine recipients, and estimate incidence rates of prespecified safety topics of interest among MFLUSIVA vaccine recipients using secondary healthcare data in the US.
- Assess the risks of GBS and myocarditis/pericarditis/myopericarditis using a self-controlled risk interval (SCRI) design by comparing the incidence rate of events during the prespecified postvaccination risk window with the incidence rate of events during a prespecified post-vaccination control window. Individuals with a history of the outcome during the prespecified outcome-specific washout period will be excluded. The washout period will be specified in the study protocol.
- Assess the risk of all-cause mortality using an active comparator cohort design, by comparing the incidence rate of events among MFLUSIVA vaccine recipients with the incidence rate among matched recipients of other licensed influenza vaccines. If causes of death can be reasonably classified as specified or unspecified, the study will also describe the incidence of deaths due to any specified underlying cause (composite mortality outcome comprising deaths with sufficient information to determine the underlying cause of death) and deaths without a specified underlying cause.

3.3. Study population and study duration

Recipients of MFLUSIVA in adults aged ≥ 50 years will be identified from the included secondary data source(s) over at least one full influenza season after the product is marketed in the US.

If uptake of MFLUSIVA is slower than anticipated, the data accrual period may be extended to include additional influenza seasons, to ensure reasonable numbers of vaccinated individuals for the planned analyses.

Individuals with a history of the outcome during the prespecified outcome-specific washout period will be excluded. The washout period will be specified in the study protocol.

3.4. Proposed outcomes of interest and risk windows

The proposed risk windows or follow-up periods postvaccination for each outcome are summarized in Table 1 below.

A feasibility assessment will be conducted for death outcomes to evaluate the completeness of mortality ascertainment, the availability of information on the underlying cause of death, and the need for linkage to external data sources to capture cause-of-death information.

Table 1. The initially proposed risk windows or follow-up periods postvaccination for each outcome in Study mRNA-1010-P901

Safety Topic of Interest	Risk Window or Follow-Up Time (Days)
GBS	1-42
Myocarditis/pericarditis/myopericarditis	1-7
Death	1-181

Note: Day 0 is defined as the date of vaccination with MFLUSIVA or the matched active comparator influenza vaccine.

Source: mRNA-1010-P901 Study Synopsis (Version fv1.0, dated July 24, 2026, submitted to BLA 125869/0.105)

3.5 Study data sources

Moderna will issue a Request for Proposal (RFP) to potential data and scientific service providers to identify and select the data source(s) best suited to fulfill this post-marketing commitment (PMC).

Data source selection will be primarily driven by evaluation of fitness for purpose and feasibility and will be guided by frameworks for real-world data (RWD) fit-for-purpose assessment published by the US Food and Drug Administration and other research groups.

The study is anticipated to utilize at least one large US secondary healthcare database with adequate capture of healthcare data for the proposed indicated population of adults aged ≥ 50 years.

To the extent feasible, data accrued through the postmarketing requirement (PMR) study (mRNA-1010-P910) will be leveraged.

The final data source(s) and the rationale for their selection will be described in the study protocol.

3.6 Proposed study milestones

Moderna initially proposed the following milestones for this PMC study:

Final Protocol: December 15, 2026

Study Completion: December 31, 2030

Final Report: December 15, 2031

“Study completion” is defined as the time at which all analytic data, including data obtained through linkage to external data source(s) for mortality ascertainment, are complete, enabling the database to be finalized and the planned analyses to begin.

Reviewer comments:

For MFLUSIVA, both OVR and [REDACTED] reviewed the available safety data in the context of these statutory criteria. Based on that review, we concluded that the current evidence does not suggest a known serious risk, a signal of a serious risk, or an unexpected serious risk related to the use of MFLUSIVA. For further discussion on the assessment of the imbalance of unspecified deaths, please see the June 18, 2026 VRBPAC meeting briefing document and FDA presentation as well as the clinical reviewer’s memorandum for this original BLA.

Given that the statutory criteria for a safety PMR are not met, OVR and [REDACTED] recommended that this additional postmarketing safety study for MFLUSIVA be pursued as a postmarketing commitment rather than as a requirement.

In response to BLA 125869/0: IR CBER IR #85 - Safety-Related PMC from July 29, 2026, (received under BLA Number 125869 Sequence No. 0110 on July 29, 2026) the Sponsor acknowledged and accepted the following revised milestones:

Final Protocol Submission: December 31, 2026

Study Completion Date: December 31, 2030

Final Report Submission: December 31, 2031

In response to BLA 125869/0: IR #86 - PMC Study Synopsis for mRNA-1010-P901 from July 30, 2026 (received under BLA Number 125869 Sequence No. 0113 on July 31, 2026), the Sponsor agreed to revising the risk window (follow-up time) of the endpoint of death from Day 1-181 to Day 0-181.

Moderna also agreed to the following:

- Using individual risk windows for the evaluation of each of the endpoints of myocarditis, pericarditis and myopericarditis individually and for the overall

myocarditis/pericarditis/myopericarditis endpoint for a risk window spanning 7 days postvaccination.

- Including in the final mRNA-1010-P901 protocol provisions for a secondary/sensitivity analysis for each of the endpoints of myocarditis, pericarditis and myopericarditis individually and for the overall study endpoint of myocarditis/pericarditis/myopericarditis using a wider risk window spanning 42 days postvaccination.

However, Moderna referred to the limitations of the secondary healthcare to reliably establish the temporal sequence between vaccination and event onset when both occur on the vaccination date (Day 0) and recommended the exclusion of Day 0 from the risk windows used for the assessment of the endpoints of myocarditis, pericarditis and myopericarditis.

(b) (6) considered the responses acceptable and will continue further discussions with Moderna during protocol development of Study mRNA-1010-P901.

The [REDACTED] concurred with (b) (6) recommendation that Moderna conduct a safety PMC study to actively monitor prespecified safety topics of interest should MFLUSIVA be approved (refer to the minutes document from the July 31, 2026, (b) (6) meeting).

On August 4, 2026, FDA and the Sponsor held an informal meeting to discuss the proposed Safety-Related Postmarketing Commitment (PMC) for mRNA-1010. As a follow-up to the August 4, 2026, teleconference, the Sponsor provided an updated study title and study description for the Safety-Related PMC, as shown below (BLA Number 125869 Sequence No. 0118):

Title: Post-Authorization Active Surveillance Safety Study to Monitor Real-World Safety of MFlusiva (mRNA-1010) Vaccine for the Prevention of Influenza Disease in the United States. Version: fv2.0, August 04, 2026.

Study Description: This will be a post-authorization safety study to evaluate deaths in a randomized population and an observational study for safety outcomes including myocarditis, pericarditis, myopericarditis, and Guillain-Barré Syndrome after receipt of MFlusiva.

Additional protocol revisions, as appropriate, will be submitted in a subsequent post-approval submission.

4. CONCLUSIONS AND RECOMMENDATIONS:

(b) (6) recommendation for a safety PMC study reflects the available safety data and aligns with the regulatory framework established under the Food and Drug Administration Amendments Act of 2007 (FDAAA). Continued monitoring through a PMC is appropriate, whereas a Title IX safety PMR is not warranted at this time.

Should this product be approved, please see the final agreed-upon milestone dates and study description in the Approval Letter.

(b) (6) will review the Final PMC Study Protocol when available.