



MEMORANDUM

Date: 24 January 2026

From: David C. Kaslow, MD, Director, Office of Vaccines Research and Review (OVRR)

Subject: OVRR Position on Filing Decision for BLA 125869 - Influenza Vaccine, mRNA (b) (4) ; mRNA-1010.4)

To: Vinay Prasad, MD, MPH, Center Director, Center for Biologics Evaluation and Research (CBER)

BOTTOM LINE UP FRONT (BLUF)

OVRR OD¹ recommends filing BLA 125869 without major deficiencies. The application meets minimum filing standards under SOPP 8404 and contains adequate scientific data for substantive review, including complete clinical data from a well-designed, adequately powered study demonstrating statistical superiority to an FDA-licensed comparator. OVRR OD acknowledges CBERR's concerns regarding the use of Fluarix as comparator in participants ≥65 years of age, where CDC preferentially recommends high-dose or adjuvanted vaccines. However, OVRR OD concludes that this comparator selection constitutes a review issue rather than a fundamental deficiency that prevents meaningful scientific evaluation.

BACKGROUND

Reference is made to:

- CBERR Round Robin on 20 January 2026 to discuss the file-ability of BLA 125869 - [Presentation](#)



RR260120 BLA
125869 Moderna Flu.

- [Meeting Summary](#)



RR 260120
BLA125869 Moderna

- Review Team Memorandum



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¹ **N.B.** OVRR Office Director (OVRR OD) takes full and sole responsibility and accountability for contents and judgments expressed herein.

- [Section 351 of the Public Health Service Act \(42 U.S.C. 262\)](#) that provides FDA authority to:
 - License biological products for interstate commerce
 - Ensure biologics are safe, pure, and potent
 - Require adequate and well-controlled investigations to demonstrate effectiveness²
 - Prevent introduction of adulterated or misbranded biologics into interstate commerce
- [21 CFR 601.2](#) that establishes specific requirements for BLA submissions, including but not limited to:
 - Manufacturing information ensuring product quality
 - Proposed labeling providing adequate directions for use
- [21 CFR 201 Subpart A](#) that addresses product labeling, requiring that:
 - Product labeling be truthful and not misleading
 - Adequate directions for use be provided
 - Contraindications and warnings be appropriately disclosed
- [21 CFR 600.3\(s\)](#) that interprets potency of biologics to mean the specific ability or capacity of the product to effect a given result, as indicated by:
 - Appropriate laboratory tests, or
 - Adequately controlled clinical data obtained through the administration of the product in the manner intended
- [FD&C Act section 505\(d\) \(21 U.S.C. § 355\(d\)\)](#) that defines “substantial evidence” and the grounds for refusing to approve an application³
 - **N.B.** Although the definition of “substantial evidence” applies specifically to drugs, FDA has also generally applied the definition to biologics⁴
- [21 CFR 314.126\(b\)](#) that defines characteristics of adequate and well-controlled studies, including but not limited to active treatment concurrent control
 - **N.B.** Although specifically applies to drugs, the characteristics have also generally been applied to biologics

DESIRED OUTCOME

Alignment between CBER OCD and OVRP on the filing decision for BLA 125869, with clear documentation of the regulatory rationale supporting the chosen pathway consistent with statutes, code of federal regulations, and established FDA filing standards while addressing reasonable scientific and ethical concerns.

² In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would, with limited exceptions, consist of controlled clinical investigations as defined in the provision for “adequate and well-controlled studies” for new drugs (21 CFR 314.126) (see former 21 CFR 601.25(d)(2) (2015) (revoked as no longer necessary, 81 FR 7445 (Feb. 12, 2016))). We note that, in section 123(f) of FDAMA, Congress also directed the agency to take measures to “minimize differences in the review and approval” of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FD&C Act. (Source: [Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products | FDA](#))

³ “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

⁴ Under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. § 262) licenses for biologics have been issued only upon a showing that the products are “safe, pure, and potent.” Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). FDA has also generally considered “substantial evidence” of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act (see also Footnote 2).

PROBLEM STATEMENT

Whether use of Fluarix as an active comparator in Study P304, particularly for participants ≥ 65 years of age where CDC preferentially recommends specific vaccines (i.e., [Fluzone High-Dose](#), [Fluad adjuvanted](#), or [Flublok recombinant](#)), constitutes a filing deficiency that prevents meaningful scientific review or a review issue that can be addressed during standard evaluation processes.

KEY UNDERLYING ASSUMPTIONS AND REGULATORY CONTEXT

- **Regulatory Intent:** Biologics License Applications (BLAs) are a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2).⁵
- **Regulatory Authority:** Section 351 of the Public Health Service Act and 21 CFR 601.2 authorize FDA to ensure biologics are safe, pure, and potent, but does not extend authority to regulating the practice of medicine or defining or dictating clinical care standards. FDA/HHS regulatory authority is product- and population-focused, not practice-focused (i.e., “FDA regulates products, not the practice of medicine”).^{6,7,8}
- **Scientific Validity of Study Designs:** Adequate and well-controlled studies can use various comparator strategies while maintaining scientific integrity
- **Scientific Adequacy of Comparator:** Fluarix remains an FDA-licensed vaccine approved for use in adults ≥ 50 years of age, including adults ≥ 65 years of age, with demonstrated efficacy in CDC observational data and prior comparative studies.
- **Scientific Adequacy of Study Evidence:** Demonstrated superiority to a concurrent FDA-licensed comparator vaccine would generally provide a basis for qualified experts to fairly and responsibly conclude that the vaccine is effective for the endpoint on which superiority was demonstrated.
- **Filing Standards:** Per CBER SOPP 8404, refuse-to-file decisions are reserved for submissions with fundamental deficiencies that prevent meaningful scientific review, not for reassessing submitted study design choices, if submitted studies comply with characteristics of regulatory standards for “adequate and well-controlled studies”
- **Regulatory Consistency:** To not appear arbitrary and capricious, filing decisions will align with statutory authority, established policies and procedures, and reasonableness, absent compelling bases for abruptly “changing the goalposts.”

HIGH-LEVEL SUMMARY OF DISCUSSION

CBER OCD Round Robin Presentation (20 January 2026)

Discussion focused on two primary concerns:

⁵ [Biologics License Applications \(BLA\) Process \(CBER\) | FDA](#)

⁶ Public Health Service Act authority is generally understood as product- and population-focused, not practice-focused.

⁷ **Statutory Limitation:** The Federal Food, Drug, and Cosmetic Act⁷ and Public Health Service Act⁶ specifically limit FDA authority to product regulation, excluding regulation of medical practice; **State Police Powers - Primary Authority:** States have primary legal authority to regulate medical practice, per Tenth Amendment and “state police powers;” **Practical Distinction:** FDA regulates what products can be marketed and how they are labeled; healthcare providers retain discretion in treatment decisions; **Precedential Consistency:** FDA has consistently maintained a distinction between product regulation and practice of medicine, providing product information while deferring to clinical judgment in treatment decisions.

⁸ 21 U.S.C. § 396 — “Practice of Medicine”: “Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease...” **N.B.** Refers to “device.”

- **Control Arm Adequacy:** CBER OCD raised significant concerns about use of Fluarix as comparator for adults ≥65 years of age, noting that high-dose flu vaccines have been preferentially recommended by CDC since 2014. CBER OCD characterized the pivotal Phase 3 clinical efficacy study as inadequate and unethical, using analogies from cardiology (TPA vs. stenting for STEMI) and oncology to argue the study failed to meet "adequate and well-controlled" standards.
- **Influenza B Efficacy:** Limited influenza B cases resulted in wider confidence intervals, though this was acknowledged as a secondary concern.

Review Team Memorandum

Review Team provided comprehensive justification for filing based on four key points:

- **Fluarix Effectiveness:** Unpublished CDC real-world effectiveness data demonstrate Fluarix remains effective in adults ≥50 years of age, with absolute vaccine efficacy comparable to other standard-dose vaccines and similar effectiveness to Fluzone HD in overlapping age groups.
- **Basis of ACIP Recommendation:** CDC preferential recommendation relies primarily on observational studies with overall low certainty of evidence. Most reliable data came from RCTs previously reviewed for product approval, with significant consideration of "potential benefits" rather than objective demonstrated benefits.
- **Prior FDA Agreement:** April 2024 Type D responses indicated the study design was "adequate and well-controlled to the extent agreed to previously with the applicant by the Division."
- **Regulatory Precedent:** Similar comparator strategies supported approval of Flublok, which used Fluarix as comparator in its confirmatory rVE study for adults ≥50 years.

Meeting Summary

From meeting summary, CBER OCD expressed strong reservations while acknowledging practical constraints:

- **Ethical Concerns:** Characterized the control arm as inadequate and unethical for ≥65 population
- **Regulatory Principle:** Emphasized ending the practice of using inferior control arms
- **Practical Recognition:** Acknowledged Review Team position regarding 50- through 64-year-old age group where Fluarix remains appropriate
- **Compromise Consideration:** Indicated willingness to consider filing with major deficiencies noted in Day 74 Letter
- **Documentation Request:** Detailed memo outlining Review Team and OVRP position and rationale

OPTIONS FOR CONSIDERATION

Option 1: File Without Major Deficiencies (OVRP Recommended)

- **Advantages:**

- **Scientific Adequacy:** Study P304 demonstrates superiority (rVE 26.6%) with adequate statistical power and appropriate endpoints
 - **Efficient Review Process:** Allows immediate progression to substantive scientific evaluation without administrative delays
 - **Regulatory Clarity:** Maintains clear distinction between filing standards and review issues
 - **Policy Stability:** Avoids abrupt change in policy for refuse-to-file based on comparator optimization rather than fundamental scientific flaws
 - **Applicant Reliance:** Honors prior FDA guidance and Type D meeting agreements
 - **Innovation Access:** Facilitates timely review of novel mRNA influenza vaccine technology
 - **Regulatory Consistency:** Maintains alignment with SOPP 8404 filing standards that focus on fundamental deficiencies preventing review
- **Disadvantages:**
 - **Scientific Limitation:** Review based on superiority to Fluarix would not provide direct evidence of comparative effectiveness versus CDC preferentially recommended vaccines in adults ≥ 65 years of age, potentially limiting information available for clinical decision-making and necessitating additional studies or real-world evidence generation
 - **Perceived Endorsement:** May appear to validate suboptimal study design choices
 - **Ethical Concerns:** Does not directly address CBER OCD concerns about participant randomization to potentially inferior treatment
 - **Policy Risk:** Might not sufficiently discourage future sponsors from selecting comparators that may be perceived as lower performing
 - **Public Health Messaging:** Could signal weak FDA commitment to optimizing study designs to answer important policy PICO questions⁹

Option 2: File With Major Deficiencies (OVRN Next Best Alternative)

- **Advantages:**
 - **Formal Documentation:** Creates official record of FDA concerns in Filing Letter Notification while allowing review to proceed on priority review timeline [through Applicant's use of a priority review voucher (PRV)]
 - **Early Applicant Notification:** Day 74 Letter provides Applicant opportunity to address issues early in review cycle, providing the Applicant an opportunity to maintain original goal date consistent with their PRV use while flagging significant concerns
 - **Review Guidance and Alignment:** Provides framework for Review Team in addressing comparator issues during review
 - **"Middle Way" Position:** Balances CBER OCD concerns with review efficiency
 - **Regulatory Flexibility:** Allows for potential indication modifications or labeling restrictions
 - **Stakeholder Communication:** Signals FDA awareness of study limitations to external stakeholders [through posting of Summary Basis of Regulatory Action (SBRA)], if approved
- **Disadvantages:**
 - **Resource Allocation:** Diverts review resources to administrative processes rather than scientific evaluation

⁹ [Chapter 4: Formulating PICO Questions | ACIP GRADE Handbook | CDC](#)

- **Regulatory Confusion:** Blurs distinction between filing and review standards
- **Administrative Burden:** Requires additional correspondence and documentation without clear regulatory basis
- **Delayed Resolution:** Could unnecessarily extend review timeline for issues addressable through standard review
- **Inconsistent Application:** May not align with historical use of major deficiency letters
- **Policy Uncertainty:** Creates ambiguity about when major deficiency letters are appropriate

Option 3: Refuse to File

- **Advantages:**
 - **New CBER Standards Communication:** Sends clear message about new CBER OCD requirements for (vaccine) study design
 - **Ethical Alignment:** Directly addresses CBER OCD concerns about participant welfare and study ethics
 - **Comparator Selection Rigor:** Demonstrates CBER OCD commitment to use of comparators based on current practice of medicine
 - **Regulatory Standard Definition:** Exercises FDA's discretionary authority to more clearly define "adequate and well-controlled studies"
 - **Future Deterrence:** May encourage sponsors to select highest performing comparators in future studies
 - **Public Health Impact:** Prioritizes optimal evidence generation for policy and clinical decision-making
- **Disadvantages:**
 - **Regulatory Inconsistency:** Contradicts precedent set by Flublok approval using identical comparator strategy¹⁰
 - **Policy Risk:** Could create regulatory uncertainty on the basis for a refuse-to-file for any comparator selection
 - **Regulatory Overreach:** May exceed statutory authority by regulating clinical practice standards rather than product characteristics
 - **Potential Applicant Prejudice:** Contradiction to prior FDA guidance and regulatory advice, creating a potential allegation of being arbitrary and capricious
 - **Potential Vulnerability:** May be seen to exceed FDA's statutory authority and risk legal challenge that could ultimately weaken regulatory authority
 - **CBER SOPP 8404 Inconsistency:** Does not meet established criteria for fundamental deficiencies preventing meaningful review
 - **Administrative Burden:** Triggers mandatory Type A meeting and potential file-over-protest process, which would incur significant opportunity costs and resource inefficiencies
 - **Innovation Delay:** Postpones review of potentially beneficial mRNA vaccine technology that may be needed in the event of an influenza pandemic
 - **Scientific Loss:** Prevents evaluation of valuable efficacy and safety data from large, well-conducted study

¹⁰ OVRD OD acknowledges that regulatory standards appropriately evolve based on scientific advances and accumulated experience. The question is whether this case presents sufficient justification for prospective standard refinement and whether such refinement should be applied retrospectively to this application given prior FDA guidance.

- **Ethical concerns:** May engender ethical questions about scientific loss and concerns from the ~40,000 study participants

Comparative Summary of Options

Criterion	Option 1: File Without Deficiencies	Option 2: File With Deficiencies	Option 3: Refuse to File
SOPP 8404 Alignment	High meets filing standards	Medium stretches deficiency definition	Low questionable fundamental deficiency
Regulatory Consistency	High aligns with precedent	Medium creates new approach	Low contradicts precedent
Scientific Review Adequacy	High permits meaningful review	High permits meaningful review	N/A prevents review
Statutory Authority	High within clear FDA authority	Medium within authority but novel application	Low potential overreach concerns
Resource Efficiency	High immediate review	Medium additional administrative steps	High If applicant does not protest Low If file over protest; significant resource diversion
Addresses CBER OCD Concerns on Fluarix	Low defers to review	Medium formal documentation	High direct response
Addresses CBER OCD Ethical Concerns	Low not addressed	Low not addressed	High prevents perceived ethical issue
Policy Clarity	High maintains clear standards	Low creates ambiguity	High establishes new standard
Applicant Fairness	High honors prior guidance	Medium allows review to proceed	Low contradicts prior guidance
Public Health Emergency Preparedness	High enables timely review	Medium enables review with documentation	Low delays potential benefit
PICO Evidence Generation (long-term)	Low maintains current status quo	Medium questions current status quo	High challenges current status quo

OVRR OD RECOMMENDATIONS AND RATIONALE

OVRR OD Recommendation: File Without Major Deficiencies

OVRR OD recommends filing BLA 125869 without major deficiencies as the regulatory action most consistent with established filing standards, SOPP 8404, FDA's statutory authority, and

prior FDA guidance to the applicant. This approach enables comprehensive scientific review while preserving the distinction between filing standards and approval standards.

- **Regulatory Basis:** Aligns with FDA's statutory authority and SOPP 8404 requirements, based on the Review Team assessment and OVRD OD concurrence that, *on its face*, the application contains adequate information for meaningful scientific review, including:
 - Complete clinical data from well-designed, adequately powered study
 - Demonstrated statistical superiority with clinically meaningful effect size
 - Comprehensive safety database from 40,000+ participants
 - Appropriate manufacturing and quality information
 - Proposed labeling with adequate directions for use
- **Scientific Justification:** Study P304 meets criteria for adequate and well-controlled investigation:
 - Randomized, observer-blind design with appropriate stratification
 - Clinically relevant primary endpoint (RT-PCR-confirmed ILI)
 - Pre-specified statistical analysis plan with appropriate success criteria
 - Active comparator with established efficacy in target population
 - Adequate sample size and follow-up duration
- **Policy Consistency:** Filing BLA 125869 maintains regulatory consistency with:
 - Historical filing decisions based on fundamental adequacy rather than study optimization to answer policy PICO questions
 - Flublok approval using identical comparator strategy
 - FDA's role as product regulator rather than clinical practice authority
- **Practical Considerations:** Filing enables comprehensive review addressing:
 - Age-specific efficacy and safety analyses
 - Appropriate indication and labeling considerations
 - Benefit-risk assessment across different populations
 - Postmarketing study requirements if warranted

Limitations of OVRD OD-Recommended Approach

OVRD OD acknowledges CBER OOD's legitimate concerns about comparator selection and proposes addressing the limitations associated with the File Without Major Deficiencies recommendation, through rigorous review:

- **Age-Stratified Analysis:** Conduct detailed evaluation of efficacy and safety data for 50 through 64 years of age and ≥65 years of age subgroups, assessing whether effect sizes differ by age and whether data support approval across all ages
- **Benefit-Risk Assessment:** Perform comprehensive benefit-risk evaluation considering:
 - Magnitude of efficacy benefit versus Fluarix
 - Safety profile including reactogenicity
 - Uncertainty regarding comparative effectiveness versus high-dose vaccines
- **Labeling Considerations:** Evaluate whether labeling should:
 - Include age-specific efficacy data
 - Note that comparative effectiveness versus high-dose vaccines is unknown in adults ≥65 years of age
 - Provide information enabling informed clinical decision-making

- **Indication Refinement:** If age-stratified data show insufficient efficacy in ≥65 subgroup, we will consider age-restricted indication pending additional studies
- **Postmarketing Studies:** Consider requesting postmarketing studies to address evidence gaps:
 - Head-to-head comparison with high-dose vaccine in ≥65 years of age
 - Real-world effectiveness studies
 - Long-term safety monitoring

OVRD OD acknowledges that filing without deficiencies may not fully address legitimate CBER OCD concerns. OVRD OD also recognizes that the submitted data may not optimally inform clinical decision-making for adults ≥65 years of age. However, OVRD OD commits to rigorous review-phase evaluation of these limitations and to earnestly consider product labeling and/or postmarketing studies to address these evidence gaps.

Next Best Alternative Recommendation: File With Major Deficiencies

If CBER OCD requires formal documentation of CBER OCD concerns, File With Major Deficiencies provides a structured approach, while maintaining review efficiency.

The Day 74 Letter could focus on:

- **Specific Deficiencies:**¹¹
 - CBER OCD concerns about the use of Fluarix comparator for ≥65-year-old age group relative to CDC preferential recommendations
 - Need for enhanced benefit-risk assessment considering available treatment alternative
 - Potential labeling implications requiring age-specific considerations
- **Review Expectations:**
 - Detailed analysis of age-stratified efficacy and safety data
 - Comparison with available effectiveness data for preferentially recommended vaccines
 - Consideration of indication refinements or labeling restrictions
 - Assessment of postmarketing study needs

OVRD OD CONCLUSIONS AND ADDITIONAL RECOMMENDATIONS

OVRD OD posits that the filing decision for BLA 125869 should be based on whether the submission contains adequate information to conduct a comprehensive scientific review of safety and efficacy. Filing review should not re-evaluate study design elements previously agreed upon during the IND phase. Any identified deficiencies should be assessed against: (1) regulatory standards for substantial evidence of effectiveness and a favorable benefit-risk profile, and (2) requirements for product labeling that provides accurate and essential information necessary for healthcare provider and patient decision-making. Such an approach is consistent with FDA's statutory authority under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and applicable regulations, while maintaining appropriate boundaries regarding the practice of medicine.

OVRD OD Recommendations for Consideration:

¹¹ Provided by CBER OCD in CBER OCD response to Review Team and OVRD OD memoranda.

- File BLA 125869 without major deficiencies as the most appropriate regulatory action that maintains consistency with established filing standards while enabling comprehensive scientific review.
- Address concerns with use of Fluarix comparator through standard review processes, including detailed evaluation of age-specific data and consideration of appropriate labeling to inform clinical decision-making.
- Confirm regulatory basis for and scope of regulating the practice of medicine; or maintain regulatory boundaries by focusing on product safety and efficacy rather than clinical practice optimization, consistent with FDA's statutory authority and constitutional limitations.
- Document regulatory rationale to ensure consistency in future filing decisions and provide clear guidance to sponsors regarding CBER expectations.
- Consider prospective guidance development for influenza vaccine studies to clarify CBER OCD expectations, while respecting appropriate regulatory boundaries and avoiding retrospective application of evolving standards.