

Center Director's Memo

Decision rendered: Refuse to File, BLA 125869 ((b) (4)) ; mRNA-1010.4; Moderna's mRNA Seasonal Influenza Vaccine)

I have read the file and heard the arguments presented by the team. It is my determination that FDA CBER will refuse to file this application. Here, I will make the arguments to support CBER OCD's position.

The Applicant (Moderna, Inc.) conducted a randomized trial of novel influenza vaccine against a standard dose comparator in adults 50 years of age and older. Years before the start of the study US FDA had approved, and CDC had preferentially recommended, three vaccines (Fluzone HD, Flublok, and Fludac) for use in individuals ≥65 years of age.

The FDA notified the Applicant of this in written communication: "...we recommend you use a vaccine preferentially recommended by the ACIP." The Applicant chose not to do so. As such, I consider the control arm beneath the prevailing US standard of care at the time of study design and conduct. Ergo, I do not consider the application to contain a trial "adequate and well-controlled" and the application is therefore, on its' face, inadequate for review.

OVRP makes several arguments to support filing and review, which I will discuss here:

1. ***The control arm used by the sponsor is better than placebo.*** To make this claim, OVRP relies on unpublished, observational data from the CDC.

Observational data are notoriously ill-suited to draw firm causal conclusions about efficacy, particularly when a natural experiment (regression discontinuity, etc.) is not used. If such study designs were reliable, we would not demand randomized trials.

But, more to the point, in my view, the argument is not relevant. The question is not whether the sponsor used a control arm better than doing nothing, but whether the control arm reflects the prevailing, U.S.-based standard of care. The answer to that question is it does not, and the Applicant was made aware of the prior ACIP recommendation.

2. ***The control arm is as good as the ACIP recommendation.*** The OVRP review team alludes to this argument writing, "While we would not draw any conclusions based solely on the results presented in the tables above, at face value they seem to support a comparable absolute vaccine efficacy between Fluarix and Fluzone HD in older adults." I disagree with this conclusion and believe it places too much weight on unpublished observational data that may suffer from residual confounding or other biases. Furthermore, the question of what ought to be recommended to older adults was based on multiple randomized trials, and has

already been adjudicated by the ACIP. I do not question the ACIP's prior determination as it is supported by high level, congruent evidence. OVRP concurs, writing about one such randomized trial, "While not powered for superiority, the data appear to support the superiority of Flublok relative to Fluarix (Table 4 below) in adults ≥ 50 ."

3. ***OVRP characterizes the ACIP recommendation as being based on potential benefits, rather than demonstrated benefits.*** Yet, I note, HD Fluzone showed a reduction in a randomized trial against laboratory confirmed influenza like illness, which is a clinical endpoint. I agree, however, that the trial suggested additional *potential* benefits. From the 2014 NEJM paper, "the effectiveness analyses signaled a favorable effect of IIV3-HD on the prevention of hospitalization, pneumonia, cardiorespiratory events, medication use, and nonroutine medical visits." While I concede that these additional benefits are only *possibly* or *potentially linked*, I view this as a tangential argument. The standard of care preferential recommendation was made-- as is always the case in medicine—by combining biological understanding (of older immune-senesce) with an interpretation of all available randomized data with clinical experience and confirmatory evidence. Given that multiple randomized studies show consistent effects, the overall recommendation stronger than many in biomedicine. Finally, OVRP actually shared this view, demonstrated when they wrote, "...we recommend you use a vaccine preferentially recommended by the ACIP."
4. ***Refuse to file would mean FDA is regulating the practice of medicine rather than the regulation of drug products.*** CBER OCD disagrees with this argument. The purpose of FDA is to regulate drug products against the U.S. landscape of available therapies. In some countries, the standard of care in the U.S. at the time of the study is not available, affordable or provided. Manufacturers may choose to conduct their trial in such countries, but doing so runs the risk that such a trial may not be considered adequate and well controlled by U.S. standards. In these cases, sponsors often anticipate this objection and themselves provide appropriate standard of care to control arm participants. That did not happen here.
5. ***The arguments presented here only concern the portion of participants in the applicants trial over the age of 65, and not ages 50-64. As such the manufacturer may wish to resubmit a BLA, using these data seeking indication in that lower age bracket.*** I note this as another argument made in favor of some filing action. Yet, as a matter of fact, data show that Flublock is

superior to Fluarix among all those over 50. Superiority would be the common interpretation of this lower bound confidence interval, even while it is from a

Table 4: Relative Vaccine Efficacy (rVE) of Flublok Quadrivalent versus Comparator against Laboratory-Confirmed Influenza, Regardless of Antigenic Similarity to Vaccine Antigens, Adults 50 Years of Age and Older, Study 2 (Efficacy Population)^{1,2}

	Flublok Quadrivalent (N=4303)		(Fluarix Quadrivalent) Comparator (N=4301)		RR	rVE % (95% CI)
	n	Attack Rate % (n/N)	n	Attack Rate % (n/N)		
All rtPCR-positive Influenza ³	96	2.2	138	3.2	0.70	30 (10, 47)

noninferiority trial. These results were known prior to the conduct of the Applicants study, and further undermine choice of control arm. Furthermore, the applicant may face post-hoc analyses challenges if they wish to partition a randomized study after the fact.

For these reasons, I believe the BLA 125869 (Moderna's mRNA Seasonal Influenza Vaccine) meets the refuse to file standard by failing to provide an adequate and well controlled study.

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