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June 27, 2023

VIA EMAIL

Members, Vaccines and Related Biological Products Advisory Committee
Food and Drug Administration
VRBPAC@fda.hhs.gov
CBERVRBPAC@fda.hhs.gov

Re: *Follow up to May 18, 2023 VRBPAC Committee Meeting – Recommendations on the Safety and Effectiveness of Abrysvo in Pregnant Women and Infants*

Dear VRBPAC Members:

We write on behalf of our client, Informed Consent Action Network ("**ICAN**"), regarding the Vaccine and Related Biological Product Advisory Committee's ("**VRBPAC**") recommendations on Pfizer's Respiratory Syncytial Virus ("**RSV**") Vaccine, Abrysvo. Prior to VRBPAC's May 18, 2023 meeting ("**May 18 meeting**") at which it made recommendations concerning Abrysvo, we submitted a letter on behalf of ICAN which raised critical issues for the committee to consider at the meeting.[1]

VRBPAC members voted 14-0 in favor when asked whether "the available data [were] adequate to support the effectiveness"[2] of Pfizer's Abrysvo maternal vaccine and 10-4 in favor when asked whether "the available data [were] adequate to support the safety"[3] of Abrysvo for expectant mothers and their babies. The "yes" votes reflect a lack of thoroughness in reviewing the data, as both questions would have been answered in the negative if the data had been properly presented and considered. Thus, we write again to bring your attention to several serious concerns regarding Abrysvo's safety and effectiveness that VRBPAC members did not properly address during the May 18 meeting.

I. EFFICACY OF ABRYSVO

As stated in our previous letter to the committee, it is crucial to note that the claimed 57.1% efficacy against "[m]edically attended RSV-associated lower respiratory tract illness ... within 90

[1] A copy of the previous letter, dated May 11, 2023, is attached hereto for convenience.

2 https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-may-18-2023-meeting-announcement at 8:01:18-8:09:00.

[3] *Id* at 8:14:00-8:19:47.

days after birth ... **did not meet the statistical success criterion**."[4] This issue seemed to go wholly unnoticed at the May 18 meeting, which focused solely on Pfizer's claim of efficacy against "severe RSV-associated lower respiratory tract illness." Because "the criterion for vaccine efficacy was not met" for this crucial second primary end point, any purported efficacy is limited and must be taken into account when doing an overall risk/benefit analysis of the vaccine which is intended for some of the most vulnerable individuals in America – pregnant women.[5]

The study itself makes clear that the vaccine, like other respiratory disease vaccines, cannot generate sterilizing immunity and that any purported efficacy against medically attended severe lower respiratory illness ("**severe LRTI**") appears to markedly wane and did so even during the short duration of the study.[6] It is not clear why this was not a major topic of concern for VRBPAC members, especially given the recent experience with the COVID-19 vaccines which also failed to generate sterilizing immunity and waned quickly and dramatically.

Another crucial issue ignored by VRBPAC was that the limited efficacy claimed by the study was assessed using relative risk reduction in lieu of absolute risk reduction. VRBPAC must be aware that this is both highly inappropriate and severely misleading in determining a risk/reward calculation for a vaccine. Absolute risk reduction is critical to gauge whether a vaccine should be administered to healthy individuals – especially vulnerable pregnant mothers. The absolute risk reduction of severe RSV and medically attended RSV, according to this study, is just 0.7% and .09%, respectively. This inadequate reduction does not justify a vote in favor of efficacy.

Lastly, the study relied upon by VRBPAC utilized incomplete and biased data to assess efficacy. As was pointed out during the public comment period,[7] Pfizer did not include all cause hospitalization or all cause LRTI hospitalization data. The only all cause data reported showed no benefit from the vaccine. Further, in both the vaccinated and unvaccinated groups, data was missing for three infants who met the study criteria for medically attended LRTI. Had this data been properly accounted for, it would have increased the cases by 50% in the vaccinated group but only by 10% in the placebo group. The omission of this data permitted Pfizer to make vaccine efficacy and confidence intervals appear significantly better than they were in reality and to

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[4] Beate Kampmann, M.D., Ph.D., et al., *Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants*, New England J. Med. 1 (Apr. 5, 2023), https://www.nejm.org/doi/pdf/10.1056/NEJMoa2216480 (emphasis added).

[5] *Id.* at 12.

[6] *Id.* at 8 (Tables); *see also* David M. Morens, et. al., *Rethinking next-generation vaccines for coronaviruses, Influenza viruses, and other respiratory viruses*, Cell Host & Microbe (Jan. 11, 2023), Vol. 31, Issue 1, 146-47("After more than 60 years of experience with influenza vaccines, very little improvement in vaccine prevention of infection has been noted. . . our best approved influenza vaccines would be inadequate for licensure for most other vaccine-preventable diseases. . . . However, as variant SARS-CoV-2 strains have emerged, deficiencies in these vaccines reminiscent of influenza vaccines have become apparent.... Considering that vaccine development and licensure is a long and complex process requiring years of preclinical and clinical safety and efficacy data, the limitations of influenza and SARS-CoV-2 vaccines remind us that **candidate vaccines for most other respiratory viruses have to date been insufficiently protective for consideration of licensure, including candidate vaccines against RSV,** a major killer of infants and the elderly." (Emphasis added)).

[7] https://www.youtube.com/watch?v=NXVMILYvocM&t=17446s.

misleadingly claim that the lower bound of its confidence interval was always above 40%.[8]

II. CONCOMITANT ADMINISTRATION OF ABRYSVO

Concomitant vaccine administration is something that should be given due consideration in making vaccine recommendations. VRBPAC failed to properly consider potential concerns related to concomitant administration of Abrysvo. Neither the FDA nor Pfizer was able to demonstrate that the vaccine remains effective when administered in conjunction with other vaccines recommended for pregnant women. As one example, VRBPAC was aware that concomitant administration of this vaccine and Tdap reduced the purported efficacy of the pertussis component of the Tdap vaccine by up to 20%-30% – meaning this vaccine could make infants more susceptible to pertussis during the very time that they are most at risk of death from pertussis, assuming Tdap is as effective as FDA claims.[9] Relatedly, the adjuvanted version of this vaccine could reduce the efficacy of the flu vaccine – a vaccine which CDC has admitted was already only 8% to 14% effective in 2021-2022[10] – by up to 20%.[11] Dr. Helen Chu, who presented on the clinical considerations of RSV in infants, called this "a major concern."[12] Aside from Dr. Chu's comment, it appeared to be a non-issue for VRBPAC when, instead, this should be seriously considered prior to any recommended approval of this vaccine.

II. SAFETY OF ABRYSVO

The issues with safety were obvious in this study, as was acknowledged by the four "no" votes with respect to the question concerning Abrysvo's safety.

Studies done by both Pfizer and GSK on their nearly identical RSV vaccines all had similar and troubling results that revealed an increased risk for preterm birth in the vaccinated group.[13] As VRBPAC members are aware, GSK withdrew its maternal vaccine program due to this data yet Pfizer's vaccine, which had equally concerning results, just received VRBPAC's green light. Dr. Paul Offit's assessment was correct that this issue "hangs over the committee" and that "FDA

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[8] The New England Journal of Medicine publication acknowledged as much: "Medically attended RSV-associated lower respiratory tract illness occurred within 90 days after birth in 24 infants of women in the vaccine group and 56 infants of women in the placebo group (vaccine efficacy, 57.1%; 99.5% CI, 14.7 to 79.8); **these results did not meet the statistical success criterion**." Beate Kampmann, M.D., Ph.D., et al., *Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants*, New England J. Med. 1 (Apr. 5, 2023), https://www.nejm.org/doi/pdf/10.1056/NEJMoa2216480(emphasis added).

[9] https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-may-18-2023-meeting-announcement at 1:43:45-1:45:00, 1:46:15-1:1:49:00. https://www.cdc.gov/pertussis/pregnant/mom/deadly-disease-for-baby.html#:~:text=In%20the%20first%206%20months,mother%20to%20help%20protect%20them.

[10] https://www.fda.gov/media/156627/download#page=12.

[11] https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-may-18-2023-meeting-announcement at 1:52:07-1:52:40.

[12] *Id.* at 1:47:45.

[13] *See* https://www.fda.gov/media/165621/download; https://www.fda.gov/media/168185/download.

should address [it]" because Pfizer's answers were wholly unconvincing.[14]

This increase in preterm births is gravely serious because, according to several VRBPAC members, including Chairwoman Dr. Hana El Sahly, if Pfizer's and GSK's data are correct, this vaccine could result in a 20% increased chance of preterm births for women.[15] As VRBPAC's members are surely aware, preterm birth can result in a number of potentially fatal issues for infants, in both the short and long term, which include patent ductus arteriosus, intraventricular hemorrhage, cerebral palsy, retinopath of prematurity, learning disabilities, and death.[16] And as both Dr. Sahly and Dr. Holly Janes stated, these studies do not even begin to reflect what the preterm birth rate may look like in the general population as opposed to the small population plagued by the healthy-user bias common in these studies.[17]

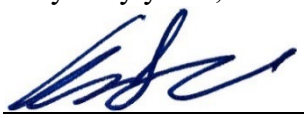
In light of the above, VRBPAC's members should have voted a resounding "no" on the issue of safety of Pfizer's Abrysvo vaccine.

III. Post-Marketing Data

While it is encouraging that VRBPAC has requested transparency and post-marketing data from Pfizer, it is unclear why its members felt comfortable voting on this product at all without transparency or, evidently, sufficient data particularly since VRBPAC does not know what the post-marketing studies will look like or if it will ever see this data. This type of "approve first, ask questions later" approach will only further the public's collapsing faith in our federal health agencies.

ICAN implores the committee to recant its recommendation of this product, demand further data, and refuse to vote until it has the data necessary to make such a significant decision on a product that will be recommended to all pregnant mothers in the United States.

Very truly yours,



Aaron Siri, Esq.
Elizabeth A. Brehm, Esq.
Catherine Cline, Esq.

Enclosure:
May 11, 2023 letter re: *May 18, 2023 VRBPAC Committee Meeting*

[14] https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-may-18-2023-meeting-announcement at 5:17:40-5:17:58.

[15] *Id.*at 7:48:58-7:54:48.

[16] *See Premature Birth*, Mayo Clinic (Feb. 25, 2023), https://www.mayoclinic.org/diseases-conditions/premature-birth/symptoms-causes/syc-20376730.

[17] https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-may-18-2023-meeting-announcement at 6:32:17-6:34:30.

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May 11, 2023

VIA EMAIL AND FDA DOCKET FDA-2023-N-1338

Members, Vaccines and Related Biological
Products Advisory Committee
Food and Drug Administration
VRBPAC@fda.hhs.gov
CBERVRBPAC@fda.hhs.gov

Re: *May 18, 2023 VRBPAC Committee Meeting – Recommendations on the Safety and Effectiveness of Abrysvo in Pregnant Women and Infants*

Dear VRBPAC Members:

We write on behalf of our client, Informed Consent Action Network (**"ICAN"**), to bring to your attention several serious concerns about the safety and effectiveness of Pfizer's Respiratory Syncytial Virus Vaccine, Abrysvo, in advance of your meeting on May 18, 2023, during which you will discuss and make recommendations concerning Abrysvo for use in infants from birth through 6 months of age by immunization of pregnant women.

Pfizer's published study concludes that, "RSVpreF vaccine [Abrysvo] administered during pregnancy was effective against medically attended severe RSV-associated lower respiratory tract illness in infants, and no safety concerns were identified." However, ICAN raises the following efficacy and safety concerns with this committee.

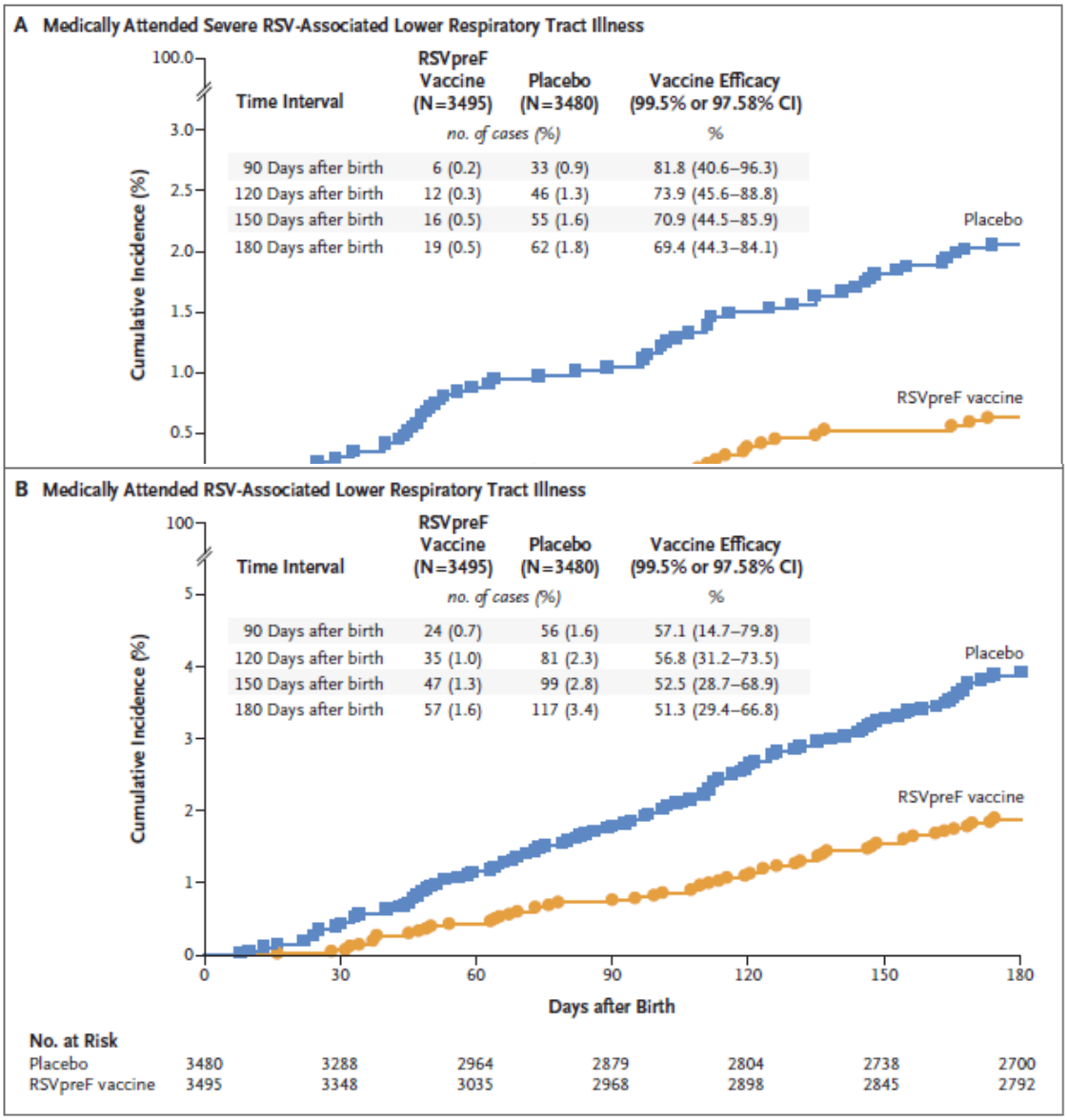
I. EFFICACY

First, it is crucial to note that the claimed 57.1% efficacy against "[m]edically attended RSV-associated lower respiratory tract illness … within 90 days after birth … **did not meet the statistical success criterion**."[1] Therefore, because "the criterion for vaccine efficacy was not met" for this crucial second primary end point (with the lower end of the confidence interval being an incredible 14.7%), **under no circumstances** should VRBPAC be relying on the results of this study to make recommendations about this vaccine for some of the most vulnerable individuals in America – infants aged three months and younger.[2]

[1] Beate Kampmann, M.D., Ph.D., et. al., *Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants*, New England J. Med. 1 (Apr. 5, 2023), https://www.nejm.org/doi/pdf/10.1056/NEJMoa2216480 (emphasis added).

[2] *Id.* at 12.

Equally concerning is that this study makes clears that the vaccine, like other respiratory disease vaccines, cannot generate sterilizing immunity and that any purported efficacy against medically attended severe lower respiratory illness appears to markedly wane even during the short duration of the study.[3]



[3] *See id.* at 8 (Tables); *see also* David M. Morens, et. al., *Rethinking next-generation vaccines for coronaviruses, influenzaviruses, and other respiratory viruses*, Cell Host & Microbe (Jan. 11, 2023), Vol. 31, Issue 1, 146-47 ("After more than 60 years of experience with influenza vaccines, very little improvement in vaccine prevention of infection has been noted. . . our best approved influenza vaccines would be inadequate for licensure for most other vaccine-preventable diseases. . . . However, as variant SARS-CoV-2 strains have emerged, deficiencies in these vaccines reminiscent of influenza vaccines have become apparent…. Considering that vaccine development and licensure is a long and complex process requiring years of preclinical and clinical safety and efficacy data, the limitations of influenza and SARS-CoV-2 vaccines remind us that **candidate vaccines for most other respiratory viruses have to date been insufficiently protective for consideration of licensure, including candidate vaccines against RSV**, a major killer of infants and the elderly." (emphasis added)).

Original antigenic sin is therefore a concern. These facts should be front and center of VRBPAC's discussion on this vaccine.

Crucially, as was the case with the Covid-19 vaccines, the study's claimed efficacy uses relative risk reduction in lieu of absolute risk reduction. This is both highly inappropriate and severely misleading in determining a risk/reward calculation for a vaccine. Absolute risk reduction is critical to gauge whether a vaccine should be administered to healthy individuals.

In this case, just 0.9% of infants in the placebo group had severe RSV 90 days after birth, whereas 0.2% did in the vaccinated group. Thus, the **absolute** risk reduction of severe RSV is just 0.7%. This means that the vaccine would purportedly allow just 7 infants per 1,000 to avoid severe RSV. Likewise, just 1.6% of infants in the placebo group had non-severe, medically attended RSV 90 days after birth, whereas 0.7% did in the vaccinated group. Thus, the absolute risk reduction of non-severe, medically attended RSV was just 0.9%, meaning that just 9 infants per 1,000 would avoid going to the doctor.

Ultimately, however, what is deeply significant is the study's finding that medically attended lower respiratory tract infection from any cause was essentially identical between the vaccine and placebo groups. As the study itself states: "RSVpreF vaccination **did not prevent** medically attended lower respiratory tract illness from any cause within 90 days after birth (vaccine efficacy, 7.0%; 99.17% CI, −22.3 to 29.3) (Table S8)."[4] If Abrysvo worked as well as is claimed in this study, one would expect an overall risk reduction for lower respiratory tract infections. This point must be considered prior to any recommendation for this population.

II. SAFETY

Although the study claims that "[n]o safety signals were detected," the study data itself belies those claims.[5] In infants, there was a 2.6% increase in any adverse event in the vaccinated group over the placebo, a 0.7% increase in severe adverse events, and a 0.3% increase in serious adverse events. In mothers, there was a 0.7% increase in the vaccinated group over the placebo, a 0.4% increase in severe adverse events, and 0.5% increase in serious adverse events.

Crucially, because the benefits of the vaccine were measured, via efficacy, for a period of three months and adverse events were measured for only one month, this had the effect of slanting the risk/benefit ratio in the vaccine's favor. But nevertheless, the safety signal is glaring with this vaccine.

The adverse events suffered by the study participants were indeed severe. In infants, adverse events included newborn transient tachypnea, respiratory distress, low birth weight, hypoglycemia, prematurity, and sepsis, the most common of which was jaundice. Yet, the study

[4] *Id.* at 8 (emphasis added).

[5] *Id.* at 1.

states that "[n]o serious adverse events in infants were considered by the investigator to be related to the vaccine."[6]

In mothers, serious adverse events included prolonged labor, premature delivery, postpartum hemorrhage, arrested labor, and gestational hypertension, the most frequent of which were preeclampsia and fetal distress. Preeclampsia is, of course, a gravely serious and life-threatening disorder that results in 16% of maternal deaths in high-income countries and 9%-26% of maternal deaths in low-income countries, as well as over 500,000 fetal deaths worldwide.[7] Alarmingly, ten mothers in the study experienced stillbirths (versus eight in the placebo group) and one vaccinated mother died from postpartum hemorrhage and hypovolemic shock.

Yet, again, the study investigator only found the following were related to the vaccine:

> Serious adverse events in four RSVpreF vaccine recipients (pain in an arm followed by bilateral lower-extremity pain, premature labor, systemic lupus erythematosus, and eclampsia — in one recipient each) and in one placebo recipient (premature placental separation) were assessed by the investigator as being related to the injection.
>
> …
>
> The only adverse events that were considered by the investigator to be related to the RSVpreF vaccine and that were reported in more than one maternal recipient in either group were lymphadenopathy and injection-site bruising (each reported in two RSVpreF recipients [<0.1%]). One adverse event (<0.1%) (prematurity) in an infant was considered by the investigator to be related to maternal RSVpreF vaccination.[8]

In terms of absolute risk/reward, for every seven cases of severe RSV the vaccine prevented (out of 1,000 vaccinated), it causes seven severe adverse events in infants; four severe adverse events and two life-threatening results in mothers; approximately nine premature births; and approximately six low birth weights. Put plainly, the risk/benefit assessment is negative. In light of this, it is deeply troubling that the authors state, "It is reassuring that no safety concerns were detected in the infants or mothers in this trial, although the number of participants was small."

It should also not be ignored that the trial excluded numerous categories of women including women with high-risk pregnancies, women who conceived through in vitro fertilization, and obese women with a BMI >40 kg/m2.

Finally, and perhaps most concerning of all, the placebo in this trial does not appear to be a true saline placebo. While the study itself does not reveal what the placebo contained, clinicaltrials.gov lists the placebo as a "biological."[9] FDA briefing documents on Pfizer's Abrysvo

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[6] *Supra* note 1, at 9.

[7] www.ncbi.nlm.nih.gov/books/NBK570611 at 1-2.

[8] *Supra* note 1, at 9-10.

[9] https://clinicaltrials.gov/ct2/show/study/NCT04424316?term=Pfizer&cond=RSV+Infection&draw=3&rank=12.

vaccine for use in individuals ages 60 and up indicates that the placebo was "a lyophile match to the vaccine, which consists of excipients matched to those used in the RSVpreF vaccine formulation, minus the active ingredients."[10] Of course, this type of flawed and unscientific study design cannot establish the actual safety profile of a vaccine because the real adverse event rate for a vaccine can only be determined by comparing subjects receiving the vaccine with those receiving an inert placebo. If indeed the same "lyophile match" placebo was used here, this casts even more doubt on the claimed lack of safety signals and sheds new serious doubt on the triumphant claims that the rates of adverse events in the vaccine group were similar to those of the placebo group.

* * *

Concerning adverse events, monitored for an extremely short time, coupled with poor and waning efficacy in this Pfizer-supported study should cause VRBPAC to seriously reconsider making any recommendations regarding this vaccine for healthy, vulnerable mothers and infants.[11]

Very truly yours,

EABrehm

Aaron Siri, Esq.
Elizabeth A. Brehm, Esq.
Catherine Cline, Esq.

[10] https://www.fda.gov/media/165623/download.

[11] *Id.* at 13.