U.S. FOOD & DRUG ADMINISTRATION

Information Request

Our Reference: STN: 125752/2

Information Request #5

Date: September 24, 2021

To: **Michelle Olsen, Ph.D.**
ModernaTX, Inc.
Email: Michelle.Olsen@modernatx.com

From: **Josephine Resnick, Ph.D.**
DVRPA/OVRR/CBER
Email: Josephine.Resnick@fda.hhs.gov

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Datasets

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have several requests for additional information regarding your datasets.

These requests have been grouped into 3 different groups based on priority and relatedness:

Priority Group #1: Comments 1-10

Please respond to these comments by **October 7, 2021**. These comments pertain to the following:

- Missing ongoing reactogenicity in the AE dataset (improperly excluded) due to multiple reasons.
    - Request for revised AE dataset, and safety analyses if applicable, that should include ongoing reactogenicity events.
- Event duration- not determined as typically done
    - Request to recalculate event duration by sensitivity analyses
- Improper Categorization of AEs
- Incorrect filename

1. The SDTM define file stylesheet has an incorrect filename (‘define1-0-0.xsl’). Please change the file name to ‘define2-0-0.xsl’ and resubmit the file.

2. In study P301, 25 subjects had AEs with an AEOUT= RECOVERED/RESOLVED or RECOVERED/RESOLVED WITH SEQUELAE, but an end date or collected duration is not provided. Please clarify if AEOUT is correctly reported (in which case an end date should be provided) or if AEOUT is incorrectly reported. Please correct the dataset accordingly.

3. In study P301, 6 subjects had AEs with an AEOUT= NOT RECOVERED/NOT RESOLVED, but an end date is provided. Please explain and correct where appropriate.

4. Regarding ongoing solicited events:

    a. We have found 2428 records in P301 in which reactogenicity events reported in CE and lasting longer than the 7-day evaluation period (CERFTDTC + 6) were not reported in the AE dataset, e.g. subject 300-2231 had myalgia from Day 3-16 as reported in CE, but myalgia was not reported in AE for this subject’s ongoing event following dose 1. Please update the AE dataset if these events should have been reported as ongoing. Please also provide revised summary safety data tables accordingly.

    b. ‘Ongoing’ was not flagged in CE as requested. Instead you flagged an event in SUPPAE with Y for ‘solicited adverse reaction’ and N for ‘AR remove flag’ (please notify us if this is incorrect), which impacts our analysis of this data. Please update the CE dataset by including ‘ongoing’ in CENRTPT with CEENTPT of ‘Day 7.’

    c. Events are listed in AE that were neither an ongoing solicited event nor an SAE, but which were categorized as ‘reactogenicity’ in AECAT. We acknowledge that you may have categorized events that were reported by the investigator which were synonymous with solicited events and which occurred during the 7-day evaluation period and which may have been merged into the CE dataset as such, but this negatively impacts out ability to analyze the data. These events should have been reported in CE from the start of the study. Please note that we requested reporting of this data in this way in our September 28, 2020 advice under your IND submission, but since this was not implemented in your November 2020 EUA

submission, we agreed that you could flag these events in SUPPAE as 'removed' from AE analysis and instead were included in the CE dataset and ultimately the reactogenicity analysis. As these events are already flagged, please revise the category for these events back to 'Adverse Event' so that they are not confused with ongoing events.

d. We have identified events that are reported in the 'Events' datasets and 'Findings About' datasets but are not connected to provide a combined assessment for the event., e.g., subject 300-2215 had lymphadenopathy reported in CE (on Days 2-null), FACE (on Days 2 and 7), AE (on Days 7-9) and FAAE (2 rows provided for event but no days are indicated). In ADARSUM the number of days for underarm gland swelling or tenderness is 2 days, which appears to be incorrect. Please correct all events in which this situation may have occurred.

5. We have identified several instances where events reported in AE were erroneously categorized as 'Reactogenicity'. For example, subject 305-2061 had a left knee torn meniscus with AECAT= Reactogenicity. Please ensure that all events in AE are characterized correctly and resubmit the AE dataset. Please note that none of the events correctly categorized as 'reactogenicity' should be included in ADAE.

6. We have identified instances where CE was not updated with the investigator collected information. For example, subject 301-2023 had severe underarm gland tenderness on Day 29 (Dose 1 day 1) in AE, and in CE the event was reported as occurring Days 30-33 with moderate severity. In ADARSUM underarm gland tenderness number of days is reported as 4 instead of 5, and the worst analysis toxicity grade is moderate. Please correct all datasets where this may have occurred and update the safety analyses results where appropriate.

7. We have identified 3290 records where 'Reactogenicity' events reported in the AE dataset have either the start date or the end date not equal to the dates reported in CE. This impacts our ability to determine the actual dates/days of occurrence, and also becomes problematic in discerning which events are ongoing. For example, erythema was reported for subject 300-2107 in which the days of the event are 31-37 in CE and 31-36 in AE (Dose 2). Please ensure consistency of the dates/days reported for each reactogenicity event in CE and AE and correct where necessary.

8. The duration of solicited adverse reactions appear to be calculated based on the number of unique days in which the event is reported. We are concerned that this underestimates the event duration (e.g. an event reported on Day 1 and Days 3 and

5 likely had lasted 5 days as opposed to 3). Please provide an analysis of solicited adverse reaction duration (as presented in Tables 14.3.1.4.1.1 and 14.3.1.4.1.2 of the CSR) where duration is calculated assuming that the event occurred continuously from the first day to the last day the event was reported (i.e. duration = last day – first day + 1), regardless of how many days the event was documented in between.

9. Please provide a rationale for reporting in the MH dataset a 'New onset type 2 diabetes' for subject US326-2100 in P301 in which the subject was vaccinated on Aug 5, 2020 and the start date of the event was Mar 26, 2021; and 'Depression' for subject US325-2195 in which the subject was vaccinated on Aug 15, 2020 and the start date of the event was Nov 3, 2020. Please report these events in the AE dataset if the dates are correct and update the safety analyses results where appropriate.

10. We have identified instances where the start date or end date of an event is missing in CE even though FACE and FAAE had each day reported. For example, 301-2053 had underarm gland swelling on Day 2, 5, 6, and 7 in FACE and on Days 9-15 in FAAE. The event for this subject was also reported in AE from Days 6-16. This event is also inappropriately reported in ADAE (note that in addition to this event not being appropriate for reporting in ADAE, it is also reported from the subject's diary as indicated in FAAE). Please update the CE dataset with the appropriate dates/days.

Priority Group # 2: Comment 11

Please respond to this comment by **October 14, 2021**, due to potential time needed to generate revised datasets.

11. We had previously requested (please refer to our PreBLA clinical comments, dated April 28, 2021) that if symptoms recorded/reported in the COVID diaries/FAEF dataset were not due to a subject having COVID-19 (negative for COVID-19 in MB), but were instead due to a solicited event occurring within 7 days post-vaccination or an unsolicited adverse event for subjects in safety subset be summarized in CE in conjunction with events reported in FACE, or in AE; and to also provide a flag that part or all of the data was from the COVID diary. We have found that this was not implemented in the datasets submitted to the BLA. For example, subject 300-2003 was determined to be COVID-19 negative on Days 1 and 3 (as reported in MB), yet the COVID-19 symptoms reported in CE under the CECAT 'efficacy' including myalgia (mild on Day 3) and fatigue (mild on Day 3) were not included with the

events under CECAT ‘reactogenicity’ which were reported as myalgia (mild on Day 2) and fatigue (mild on Days 1-2).

a. We request that the CE dataset (and FACE if that is the dataset you are using to report the ADARSUM dataset), and AE dataset be updated with this information. The FAEF should be flagged that the event is now reported in another dataset(s).

b. Please comment on whether the events reported in the FAEF dataset were included in your determination of overall rates of reactogenicity events or unsolicited AEs. If not, please provide updated safety summary tables.

Priority Group # 3: Comments 12-17

Please respond to these comments by **October 24, 2021.** These comments pertain to the following:

- Clarifications
- Inconsistent coding
- Future improvements
- Improper sub-categorizations

12. In AE, the subcategory ‘PIMMC’ is not useful as it is reported for most of the events that are categorized as AEs – e.g., upper respiratory infection, finger fracture, UTI, etc., and sometimes even reactogenicity events. Please correctly subcategorize these events in the future. If the event does not need a subcategory then AESCAT can be null. Please note that other subcategories that we are suggesting for AEs besides PIMMC is ‘NOCD’ and ‘Exacerbation of a chronic disease.’

13. Many event dates appear inconsistent between CE, FAEF, and SUPPFAEF. For example, subject 348-2303 reported Clinical and Radiographical Evidence of Pneumonia on 2021-01-14 in FAEF. However according to CE, both events started on 2021-01-21. In addition, a date of 2021-01-21 was recorded for both events in SUPPFAEF. Similarly, subject 334-2182 reported Clinical and Radiographical Evidence of Pneumonia on 2020-12-23 in FAEF, but both events were reported as having started on 2021-01-17 in CE. A date of 2021-01-17 was also recorded for these events in SUPFAEF. Please explain the discrepancies in the reported dates between these datasets.

14. Medication provided to either prevent or treat solicited events should be reported in CM instead of or in addition to SUPPVS. Please ensure that any future datasets submitted will include this information in CM.

15. It appears that you have summarized reactogenicity events in CE to include solicited events occurring within the 30 minutes to 1-hour post-vaccination time frame. Immediate solicited events should be reported in CE on a separate line from the Day 1-7 event and be categorized in CECAT as 'Immediate Reaction.' Please implement this in any future submissions.

16. Inconsistent coding was used for the exact same AE and/or MH term (see table below for example). In the Reviewer's Guide you indicate that there is no issue due to inconsistent coding. We disagree with this assessment, as inconsistent coding can impact our safety analysis. In future submissions, please ensure that you provide data with consistent coding.

aeterm	aellt	aedecod	aehlt	aehlgt	aebodsys	count_of_aes	med drav
UPPER RESPIRATORY ILLINESS	UPPER RESPIRATORY DISORDER	RESPIRATORY DISORDER	RESPIRATORY TRACT DISORDERS NEC	RESPIRATORY DISORDERS NEC	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	23
UPPER RESPIRATORY ILLINESS	UPPER RESPIRATORY INFECTION	UPPER RESPIRATORY TRACT INFECTION	UPPER RESPIRATORY TRACT INFECTIONS	INFECTIONS - PATHOGEN UNSPECIFIED	INFECTIONS AND INFESTATIONS	1	23

17. With regards to ongoing solicited events, we had previously requested that reactogenicity events lasting beyond Day 7 and collected in the 'Medical Attention Day' Form be mapped to FACE for the day-to-day information instead of FAAE. For this submission, we will not request that you update the data in FACE with the data in FAAE; however, please ensure that reactogenicity events lasting beyond Day 7 and collected in the 'Medical Attention Day' Form are mapped to FACE for the day-to-day information instead of FAAE.

Please confirm your receipt of this request, and provide your responses as amendments to STN 125742 by the dates requested for each set of comments. For comments 14 to 17, please acknowledge that you understand the expectation for future submissions with regards to the advice provided.

Please contact me if you have questions and include Sudhakar Agnihothram (Sudhakar.Agnihothram@fda.hhs.gov) and Joseph Kulinski (joseph.kulinski@fda.hhs.gov) on all communications.