U.S. FOOD & DRUG ADMINISTRATION

To: File STN BL 125752/0- Moderna-COVID-19 Vaccine, mRNA (SPIKEVAX)

From: Pete Amin, CSO, OCBQ/DMPQ/MRB2
Obinna Echeozo, Microbiologist, OCBQ/DMPQ/MRB2

Through: Anthony Lorenzo, Branch Chief, OCBQ/DMPQ/MRB2
Carolyn Renshaw, Acting Director, CBER/DMPQ
Mary A, Malarkey, Director, CBER/OCBQ

CC: Jie He, Team Lead, OCBQ/DMPQ/MRB2
Christine Harman, Team Lead, OCBQ/DMPQ/MRB2
Debra M. Emerson, CSO, ORA/OMPTO/OBPO/BPIS
Nicole Trudel, Acting Deputy Director, CBER/DMPQ

Facility: Lonza Biologics, Inc. (Lonza)

Subject: Biologics License Application (BLA) STN 125752/0 Review Memorandum of the responses to the Form FDA 483 List of Inspectional Observations issued at the conclusion of the October 18 -22, 2021 Pre-License Inspection (PLI) of Lonza Biologics, Inc. located at 101 International drive, Portsmouth, NH 03801 (FEI # 3001451441).

RECOMMENDATION

Review of the firm's responses (Amendment STN 125752/0.22) to the Form FDA 483 Observations1 through 4 appear acceptable and (b) (5), (b) (7)(E) (b) (5), (b) (7)(E) .

Summary

The Center for Biologics Evaluation and Research (CBER) and Office of Regulatory Affairs (ORA) conducted a PLI of Lonza from October 18-22, 2021, in support of BLA STN 125752/0.

The inspection team consisted of Pete Amin (PA), Consumer Safety Officer (CSO), CBER/DMPQ/MRBII, Obinna Echeozo (OE), Microbiologist, CBER/DMPQ/MRBII, and Debra M. Emerson (DE), Consumer Safety Officer (CSO), ORA/OMPTO/OBPO/BPIS. At the conclusion of the PLI on October 22, 2021, a four-item Form FDA 483, List of Inspectional Observations, was issued to the firm.

Lonza submitted a written response (Amendment STN 125752/0.22), received by CBER November 12, 2021, that outlined the proposed corrective actions to address each inspectional observation. The information was reviewed and assessed, and that assessment is summarized in this memorandum. The responses appear acceptable and (b) (5), (b) (7)(E) (b) (5), (b) (7)(E) .

Review of Lonza's Responses to the FDA Form 483 Observations
The original Form FDA 483 observations are (in italics), Lonza's responses (in regular text), and the inspector/investigator comments (in bold/italics) are provided below:

Observation 1

Investigations into deviations are not always initiated in a timely manner. There were multiple instances, where investigations were not initiated until two months from occurrence, and after drug substance batches were shipped to the filling facilities for further processing. Specifically, the following investigations are noted as being initiated after drug substance batches were shipped to filling facilities:

a) Record # 763571 – three lots for process (b) (4) *for high* (b) (4) *alarms for more than 10 minutes during unloading and loading of* (b) (4) *drug substance lots.*
b) Record # 734601 – labeling error to identify samples from five lots were mislabeled due to programming issues within electronic batch records.
c) Record # 779273 – the validated (b) (4) *during* (b) (4) *process was exceeded. Investigation noted similar deviation for multiple lots between October 2020 and March 2021.*
d) Record # 779669 – lipid materials were used in process before release due to documenting error (three lots impacted), materials status tag was missing.
e) Record # 798601 – (b) (4) *was not calibrated at required schedule due to equipment mix up. The* (b) (4) *equipment was used for multiple lots before calibration was completed.*

Lonza's Response

The firm's response acknowledges that initiation and investigation of deviations related to SPIKEVAX operations was not always performed in a timely manner. The firm attributed this to challenges experienced in adapting systems at the Portsmouth site as well as in hiring and training personnel to maintain the COVID-19 mRNA vaccine manufacturing and release schedule. In the months where the pace of production was faster than the pace of lot disposition, the outcome was a backlog of completed records pending review. Recognizing that the majority of deviations are identified during batch documentation review, delays in initiating the review process led to identification and initiation of investigations weeks after occurrence. This is reflected in the deviation management system ((b) (4) where the "Date of Occurrence" and "Date Opened" are documented.

Lonza proposed the following corrective actions:

1. Reassess the resource needs for all functional groups supporting mRNA Operations.

2. Establish standard work practice to require that each electronic batch record (eBR) used in mRNA manufacturing be reviewed by manufacturing personnel within (b) (4) days of completion; this ensures timely identification, initiation, and investigation of deviations. Records are then submitted to QA personnel who will perform a second level review within a target of (b) (4) days.
3. Define a plan to eliminate and prevent any backlog in batch documentation review and monitor these Key Performance Indicators (KPIs) during weekly COVID-19 mRNA vaccine management meetings. Deviation metrics (e.g., quantity per lot, number of overdue deviations) are reviewed during the Portsmouth Quality Council (monthly meeting) to ensure the quality system is maintained in a state of control.
4. Maintain current process whereby Lonza QA provides the customer with a summary of any major or critical batch-related deviations open in the quality system at the time of shipping under quarantine status. Additionally, any deviation discovered post shipment which has critical or major quality impact requires customer notification within (b) (4) (b) (4) (critical) or (b) (4) business days (major, with product quality impact) per the Quality Agreement between both companies; the final investigation report is subject to customer review and approval.

Lonza indicated the above actions will ensure timely detection and investigation of lot-related deviations, with appropriate oversight of performance by area and site leadership. Additionally, the actions allow the customer to be aware of significant events that occurred during batch production so they can make immediate and informed decisions for the DS and final product within their control. Lonza is not aware of any confirmed quality impact of DS lots shipped to the customer with open investigations at the time of shipment.

Lonza provided a timeline for completing the following corrective actions:

1. Reassess the resource needs for all functional groups supporting mRNA Operations: December 31, 2021
2. Establish standard work practices for electronic batch record (eBR) and batch documentation review by Manufacturing and QA personnel: January 31, 2022
3. Track and monitor KPIs for eBR and batch documentation review: January 31, 2022

Reviewer's Comments: The firm agreed to make corrective actions to ensure timely detection and investigation of lot-related deviations, with appropriate oversight of performance by area and site leadership. The firm's response appears acceptable and (b) (5), (b) (7)(E)

Observation No. 2

Human errors that occur during validation are documented as comments and not handled as deviations and investigated. Specifically, during the cleaning validation for the (b) (4) *, the first run (i.e., run #1) was invalidated due to human error: the operator forgot to document run #1 results. An additional* (b) (4) *runs were performed. Per SOP USPO-4175, "Validation Protocol Comments, Discrepancies and Deviations," human errors require only a comment to be noted.*

Lonza's Response:

Lonza acknowledges that the Standard Operating Procedure, USPO-4175, "Validation Protocol Comments, Discrepancies, and Deviations" states that Discrepancy Reports are not required for human errors, and that comments may be used to document unplanned excursions in a validation report that do not demonstrate failure to meet the pre-determined acceptance criteria.

Lonza explained that the discrepancy that occurs during validation execution is handled differently than a deviation, which would be captured in the (b) (4) deviation management system per Lonza Standard Operating Procedure USPO-1698, "Deviation Guidance and Report Completion in (b) (4) " and governing Lonza Quality Standard, CORP-54 "Deviation Management". If during the course of the validation study, it is determined a discrepancy has potential to impact product or process, a deviation record will be initiated in (b) (4) per USPO-1698.

Lonza describes that in the case of an invalid run, acceptance criteria may not be achieved due to extrinsic causes such as human error, sampling error, or documentation error. Such circumstances do not mean failure to meet pre-determined acceptance criteria. A "no run" or "invalid" event is not equivalent to a "failed run" event, due to the extrinsic nature of the event. USPO-4175 and associated form USPO-4176 will be revised to include documentation of human error on the Discrepancy Report form, as opposed to a comment in the protocol.

Lonza clarified that if an excursion occurs during process validation, a formal deviation may be initiated if it is determined there is impact to product/process and/or in the case of repeat batches. Discrepancies that occur during cleaning validation may occur during Process Performance Qualification (PPQ) campaigns but may not necessarily impact product/process if determined to be extrinsic. During equipment validation, an excursion may require a deviation if it occurs during requalification, where that equipment has been used in processing and could impact product/process. Discrepancies that occur during computer systems validation would occur prior to system (b) (4) use for production. Any discrepancies that occur during the operational phase and during production use would require a deviation in (b) (4)

Lonza proposed the following timeline for proposed corrective actions:

Revise USPO-4175, "Validation Protocol Comments, Discrepancies, and Deviations", and associated Form USPO-4176 to include documentation of human error on the Discrepancy Report form- Implementation/completion date: February 28, 2022.

Reviewer Comment: Lonza's response appears acceptable based on clarification and proposed corrective actions. (b) (5), (b) (7)(E)

(b) (5), (b) (7)(E)

Observation No. 3

The manufacturing, storage, and utility areas are not kept clean and free from dust, dirt, vermin, and other contaminants. In addition, the surfaces (walls, ceilings) are not always intact or smooth. Specifically,

a) *On 10/20/2021, ceiling and wall damage was observed in* (b) (4) *in building* (b) (4) *Cracks in the ceiling, separation of boards from the wall, exposed dry wall and peeling paint was observed. This room is used to manufacture COVID vaccine* (b) (4) (b) (4) *.*
b) *Two overhead doors (receiving door in building* (b) (4) *and overhead door* (b) (4) *in building* (b) (4) *) were observed with gaps to the outside.*
c) *Dead flies (more than 12) were observed in the entry into the air handling penthouse for building* (b) (4) *. Two exhaust vents in the penthouse were identified to not contain a screen to prevent the entry of insects*
d) *On 10/19/2021, growth like material was observed on the top of the* (b) (4) (b) (4) *in building* (b) (4)
e) *On 10/19/2021, growth like material was observed in a pan under the leaking clean steam generator in building* (b) (4)

Lonza's Response:

Lonza acknowledges the deficiencies observed in the manufacturing, storage, and utility areas during the October 2021 inspection and states that it is fully aware of the requirements to maintain GMP compliant facilities. Reducing the number of on-site personnel under pandemic conditions contributed to a lapse in oversight of manufacturing areas by Operations and QA management. Fewer walkthroughs of utility and interstitial (i.e., non-controlled, non-classified spaces external to the manufacturing suites) areas were performed by cross-functional personnel. Lonza recognizes that lack of routine Preventive Maintenance (PM) in interstitial spaces and inactive PMs in the (b) (4) facility must be addressed. The (b) (4) facility was in the process of being decommissioned at the time its buffer preparation suite was re-assigned to SPIKEVAX buffer manufacturing. Unfortunately, re-activating the PMs in that area was overlooked in the project plan.

Lonza listed corrective actions taken or will be taken:

a) Work Orders 34120173, 34351668, 34358375, 34358376, 34351082 and 34361578 were created to address elements: A, B, C, D, E (reference Attachments 1-6).
b) Reinstate (b) (4) manufacturing (b) (4) PM in the (b) (4) area ((b) (4) Definition: Cross functional group going to the place of work to view, observe and take action. This will include Engineering, Facilities, Maintenance, Utilities and Quality team members).
c) Create (b) (4) PM for Utilities and Interstitial areas that includes representatives from cross functional groups.
d) Monitor and trend maintenance Work Orders and PMs (b) (4) to ensure the manufacturing facility is appropriately maintained.
e) (b) (4) PMs to be administered through CMMS system.

Lonza will complete these actions by:

a. Element A: (b) (4) Suite Inspection- WO 34361578: November 15, 2021
b. Element B: Overhead Door Gaps – WO 34358375, 34358376: November 3, 2021
c. Element C: Install (b) (4) on Exhaust Fans – WO 34351082: October 19, 2021
d. Element D: (b) (4) – WO 34351668: October 21, 2021
e. Element E: Clean Steam Leak – WO 34120173: December 30, 2021
f. (b) (4) Manufacturing (b) (4) PM in the (b) (4) area: December 15, 2021
g. Create (b) (4) (b) (4) PM for Utilities and Interstitial areas: January 20, 2022

Lonza states that the on-the-floor presence of area and cross-functional leadership during (b) (4) PMs will provide visibility to areas needing attention and drive timely correction using the maintenance Work Order process. Completion of items b and c above will provide a complete (b) (4) PM program for the entire Lonza Portsmouth facility.

Reviewed comment: The firm's response appears acceptable and (b) (5), (b) (7)(E)
(b) (5), (b) (7)(E)

Observation 4

The facility is not maintained in a state of control in that leaking pipes and equipment are not repaired in a timely manner. Specifically, there are 109 leak repair tags for utility leaks which remain open since January 24, 2019. For example:

a) *Repair tag 12423703 was opened on July 3, 2019 for a* (b) (4) *floor drain piping issues*
b) *Repair tag 12788542 was opened on October 31, 2020 for a leak on the* (b) (4) (b) (4) *for the clean steam generator in building* (b) (4)
c) *Repair tag 12782647 was opened on October 22, 2020 for a leak on the* (b) (4) *water line.*

Lonza's Response:

Lonza acknowledges the deficiencies observed during the October 2021 inspection and states that it is aware of the requirements to complete necessary repairs in a timely manner. The site manages a high volume of repair tags for equipment located in controlled and non-controlled areas, with repairs prioritized based on severity, accessibility (location), and availability (scheduling). Repair tags for leaks represent a subset of all work orders, and maintenance personnel have closed >900 orders for leak repairs since January 24, 2019.

Lonza explained that the work management process for requesting, executing, documenting, reviewing, and tracking maintenance activities at the Lonza Portsmouth site is described in USPO-2421 "Maintenance Execution Procedure". The Maintenance Planning Group has daily and weekly meetings where open repair notifications, including leak repairs, are reviewed, and added to the scheduled work based upon priority. Open repair tags for leaks in controlled areas are also reviewed during ad hoc shutdown planning meetings.

Lonza planned the following actions to improve management oversight of facility leaks requiring repair:

a) Engineering & Maintenance personnel to review the existing action plans documented in the CMMS system for all open repair tags for leaks within the facility (109 leaks inclusive of Repair Tags 12423703, 12788542 and 12782647).
b) Update the existing action plans to reflect timelines that are prioritized and coordinated with responsible area management.
c) Complete leak repair action plans at the updated timelines.
d) Monitor and trend backlog of leak repair tags to ensure the facility is maintained in a state of control.
e) (b) (4) PM to be administered through CMMS system.

Lonza states that the on-the-floor presence of area and cross-functional leadership during (b) (4) PMs will provide visibility and drive timely repairs of leaks within the manufacturing facility.

Lonza provided the timelines for completing the corrective actions as follows:

a) Review the existing corrective action plans for the existing (109) Leak Repair Tags: December 20, 2021
b) Revise the corrective action plans for Leak Repair Tags to include timely completion dates: January 20, 2022.

Review comment: Lonza agreed to take appropriate corrective actions to improve the process for systematic and structured review of the repair backlog. The firm's response appears acceptable and (b) (5), (b) (7)(E) ***.***