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## SUMMARY

(Written by CDL)

The Center for Biologics Evaluation and Research (CBER) led a Pre-License Inspection (PLI) of Aldevron, LLC (hereafter, Aldevron) in Fargo, ND, from November 1 – 5, 2021. This PLI was conducted in support of rolling BLA (STN 125752/0) from ModernaTX, Inc. (hereafter, Moderna) for SPIKEVAX (COVID-19 Vaccine, mRNA), hereafter SPIKEVAX. Aldevron is a contract manufacturing organization (CMO) that produces linearized plasmid DNA (pDNA) for use in the manufacture of SPIKEVAX drug substance (DS). SPIKEVAX is indicated for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in persons 18 years of age and older. The current inspection was conducted in accordance with CPGM 7345.848, Inspection of Biological Drug Products (CBER). An equivalent of a Level 1 inspection was performed under Product Code 57C (Viral Vaccines) and Product Assignment Code 45848B (Pre-License Inspection – Vaccines). Inspectional coverage was provided for the Quality, Production, Facilities and Equipment, Materials, Packaging and Labeling, and Laboratory Control systems.

The current inspection was the first FDA inspection of Aldevron and included a review of records generated in support of BLA 125752/0 and walk-through inspections of the warehouse; the receiving, Quality inspection (QI), and quarantine areas; the (b) (4) (b) (4) Facility Production areas; the Aldevron storage and distribution services (ASDS) area; the Quality Control (QC) laboratories; and the shipping area. The following operations were also observed: visual inspection of starting material (b) (4) (b) (4) upstream activities (b) (4) (b) (4) downstream activities (b) (4) (b) (4) (b) (4)

Records reviewed included, but were not limited to, the following: quality event (QE) investigations; batch production records; CAPA plans; change requests; changeover procedures; cleaning and sanitization procedures; equipment logbooks; equipment cleaning validations; facility and equipment qualifications; environmental monitoring (EM) procedures and trend reports; gowning certification procedures and results; (b) (4) process simulation reports and batch records; Quality Unit policies and procedures; training records; in-process testing/controls; and related procedures, policies and/or protocols.

No inspectional observations were issued at the conclusion of the inspection; however, the following discussion items were reviewed with management during the closeout meeting:

- Gowning Procedures and Background Environments for Execution of Certain Upstream Activities
- Quality Management System (QMS) Enhancements
- Controlled Issuance of Documents and Forms
- Dedicated Production Area for Moderna Products
- Installation of (b) (4)
- Security and Access to QI and Warehouse (b) (4)
- Dedicated Storage Area for (b) (4) Final Containers
- Mold Excursions
- Mold Specifications
- Categorization of Quality Events

No samples were collected and no refusals were encountered during this inspection.

## ADMINISTRATIVE DATA

(Written by CDL)

| | |
|---|---|
| Inspected Firm: | Aldevron, LLC |
| Location: | 4055 41st Avenue South<br>Fargo, ND 58104 |
| Phone: | (701) 297-9256 |
| FAX: | (701) 280-1642 |
| Mailing Address: | 4055 41st Avenue South<br>Fargo, ND 58104 |
| Dates of inspection: | November 1 – 5, 2021 |
| Days in the facility: | 5 |

Inspectors: Christian D. Lynch (CDL), Consumer Safety Officer (CSO) – Lead Inspector, CBER/OD

Jared Greenleaf (JG), CSO- Inspector, CMC/Facility Reviewer, CBER/OCBQ/DMPQ/MRBI

Prabhu Raju (PR), CSO – Investigator, ORA/OMPTO/OBPO/BPIS

On November 1, 2021, we (CDL, JG, and PR) presented our credentials to security personnel in the (b) (4) Production facility office area. We then proceeded to the inspection conference room in the (b) (4) Production facility and presented our credentials and issued an FDA-482, Notice of Inspection, to Kevin Ballinger, Chief Executive Officer (CEO). Mr. Ballinger identified himself as the most responsible person at the site. An opening meeting was then conducted with Mr. Ballinger and the following individuals: (b) (6), (b) (7)(C)

During the opening meeting, the firm provided a PowerPoint presentation to include an overview of Aldevron (general information/culture/vision/values), a campus map with phases of development, a brief historical timeline, site organizational charts, a production summary for pDNA, a summary of the QMS and recent enhancements, facility diagrams, service level definitions (Research Grade (RG), GMP-Source, and cGMP), photos of the site, executive team background summaries, and additional Quality information. The slide deck for the opening meeting presentation is attached as **Exhibit PR1**.

No inspectional observations were issued at the conclusion of the inspection; however, a closeout meeting was conducted to review discussion items and recommendations.

The following members of the firm were present at the closeout meeting:

- Kevin Ballenger, CEO
- (b) (6), (b) (7)(C)

The following Moderna representatives also attended the closeout meeting:

- Huijuan Li, Vice President (VP), Analytical Development
- Jason Murphy, VP, Nucleic Acid
- (b) (6), (b) (7)(C)
- (b) (6), (b) (7)(C)

Each inspection team member contributed to the writing of this report and initials are used to designate individual authorship of each section.

## HISTORY

(Written by CDL)

The following timeline represents a brief historical overview of Aldevron, LLC:

- 1998 – Aldevron launched at North Dakota State University by Michael Chambers and John Ballantyne
- 2002/07 – Manufactured West Nile vaccine (b) (4) (b) (4)
- 2009 – Opened protein site in Madison, WI
- 2014 – Expanded the R&D facility at the Amber Valley Parkway location in Fargo
- 2016/17/18 – Manufactured malaria vaccine (b) (4)
- 2018 – Designated the Fargo GMP facility (also referred to as the "Breakthrough Campus") as operational
- 2020 – Manufactured a component for experimental COVID-19 vaccine
- 2020 – Fargo Breakthrough Campus facility designated as (b) (4) supplier of pDNA genetic template for Moderna COVID-19 vaccine (mRNA)
- 2021 – Opened a new 189,000 $ft^2$ GMP facility (b) (4) Production) at the Breakthrough Campus in Fargo
- 2021 – Opened a new 45,000 $ft^2$ research grade (RG) facility for production of pDNA for pre-clinical projects at the Advance Campus in Fargo
- 2021 – Completed a (b) (4) expansion at the Madison, WI, facility

The Aldevron Breakthrough Campus in Fargo is comprised of the (b) (4) Production facility, the (b) (4) Production (b) (4) facility, and (b) (4) logistics hub. As noted above, the firm has additional facilities in Fargo (Advance Campus) and Madison, WI; however, as these sites do not produce material for Moderna, they are outside the scope of this inspection. Functions conducted within the Breakthrough Campus buildings are as follows:

- (b) (4) Production Facility
  - (b) (4) mRNA manufacturing; GMP (b) (4) manufacturing (including an established (b) (4) and a dedicated area for a future (b) (4) (b) (4) and an office area
  - (b) (4) mechanical area; buffer & media preparation area; process laboratory testing; and (b) (4) separate office areas

- (b) (4) Production Facility
  - (b) (4) GMP source manufacturing; GMP (b) (4) manufacturing (including established (b) (4) office areas; and shipping
  - (b) (4) mechanical area; QC laboratories; ASDS; and (b) (4) separate office areas

- Logistics Hub
  - (b) (4) and centralized utility and distribution to GMP production lines

Aldevron, LLC, has never held a license for the U.S. market (or been inspected by the FDA prior to this PLI). As noted above, the firm offers three service levels for pDNA to include cGMP, GMP-Source, and Research Grade (R&D) materials. The firm stated that (b) (4) pDNA produced for Moderna is manufactured in the GMP production areas.

Products manufactured at the Breakthrough Campus facility include pDNA, mRNA, and recombinant proteins. To prevent cross-contamination, the firm utilizes a number of controls to include unique material numbers/lot numbers, closed systems (where possible), lot dedicated production personnel, segregated production areas/suites (with (b) (4) manufactured at a time), (b) (4) access to production suites, cleaning and changeover procedures, and single-use equipment. Open product manipulation steps are also performed (b) (4) (b) (4)

Addresses of relevant sites include the following:

<u>Aldevron, LLC – Corporate Headquarters – Breakthrough Campus</u>

4055 41st Avenue South
Fargo, ND 58104

(b) (4)

(b) (4)

Approximately (b) (4) people are employed at the Breakthrough Campus. This includes (b) (4) employees in Quality and (b) (4) in Operations, Finance, and Human Resources (HR).

Operating hours are from (b) (4) Site operations may (b) (4)

All post-inspectional correspondence should be directed to:

(b) (6), (b) (7)(C)
Aldevron, LLC
4055 41st Avenue South
Fargo, ND 58104
Tel: (b) (6), (b) (7)(C)
Fax: (b) (6), (b) (7)(C)
Email: (b) (6), (b) (7)(C)

## INTERSTATE COMMERCE

(Written by PR)

A list of manufactured pDNA (Moderna Construct (b) (4) Lots) is included in **Exhibit PR6**. The pDNA lots can be shipped to either Lonza Biologics, Portsmouth, NH; ModernaTX, Inc., Norwood, MA; (b) (4) (b) (4) These sites are all considered drug substance manufacturers and are listed in **Exhibit PR18**. The fill/finish sites for Moderna's COVID-19 Vaccine are also listed in **Exhibit PR18** and includes Catalent and Baxter facilities in Bloomington, IN.

## JURISDICTION

(Written by PR)

No licensed biological drug substances or drug products are manufactured at this site. This site contract manufactures linearized plasmid DNA (pDNA, Moderna Construct (b) (4) (b) (4) for ModernaTx, Inc., 200 Technology Square, Cambridge, MA 02139.

## INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

(Written by CDL/PR)

An Organizational Chart for the Aldevron Breakthrough Campus is attached as **Exhibit PR1, page 8**. Kevin Ballinger, Chief Executive Officer, joined the firm in 2020 and is the most responsible person onsite. (b) (6), (b) (7)(C) is the (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and reports directly to Mr. Ballinger. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and also reports directly to Mr. Ballinger. (b) (6), (b) (7)(C) all report directly to (b) (6), (b) (7)(C) (b) (6), (b) (7)(C)

Individuals that were interviewed during the inspection are listed in the following table:

| Name | Job Title |
|---|---|
| Kevin Ballinger | Chief Executive Officer |
| (b) (6), (b) (7)(C) | (b) (6), (b) (7)(C) |
| Luke Kroger | Director, GMO-S Manufacturing & Production |
| (b) (6), (b) (7)(C) | (b) (6), (b) (7)(C) |
| Jason Murphy | VP of Nucleic Acid (Moderna) |
| (b) (6), (b) (7)(C) | (b) (6), (b) (7)(C) |

| Name | Job Title |
|---|---|
| (b) (6), (b) (7)(C) | (b) (6), (b) (7)(C) |
| Angelica Meyer | Manager, Technical Operation |

During the inspection, (b) (6), (b) (7)(C) functioned as the primary inspection facilitators. Each processed inspector requests, coordinated site walk-through inspections, and ensured that appropriate personnel and records were available to address our questions.

**FIRM'S TRAINING PROGRAM**

(Written by CDL)

I reviewed the firm's training program with relevant personnel including Standard Operating Procedure (SOP)-QS-0010 – "Personnel Training". This SOP applies to all Aldevron employees (including temporary employees, consultants, and contractors) that have roles in manufacturing under the firm's QMS. Noteworthy requirements from the SOP are listed below:

- Creation of (b) (4) training plans – (b) (4) plans include (b) (4)

- Training plan/curriculum maintenance – current training plans should be maintained for employees; management must review plans for appropriateness (b) (4)
- Training execution – includes the following methods: (b) (4) (b) (4)
    - For (b) (4) training (b) (4) requirements (b) (4) is required: (b) (4) (b) (4)
- (b) (4)
- Requalification training – employees that support (b) (4) processes (e.g., (b) (4) requirements to participate in a (b) (4)
- Additional training steps include (b) (4)

(b) (4) training for pDNA production operators also includes (b) (4) (b) (4)

Employee training records are maintained with a hybrid approach that includes both paper and electronic records. The firm utilizes a training (b) (4) (b) (4) training, and other training requiring the (b) (4) Paper records are utilized to document in-process and other training activities. When complete, paper training records are submitted to Quality Systems Document Control for subsequent filing into individual training binders. A draft version of SOP-QS-0010 was provided during the inspection. In the draft SOP, Step (b) (4) (Training Record Maintenance) was revised to require that completed training records (b) (4) (b) (4)

During the inspection, I reviewed the training records for (b) (6), (b) (7)(C) (upstream operator) and (b) (6), (b) (7)(C) (b) (4) operator). The training binders for each operator appeared to be complete (and up to date) with appropriate documentation for all required training.

**MANUFACTURING OPERATIONS/INSPECTIONAL COVERAGE**

**Manufacturing Overview**

(Written by CDL)

The upstream operations for manufacture of the (b) (4) construct begin with a (b) (4)

(b) (4)

(b) (4)

(b) (4)

**Facility Walk-Through Inspections**

(Written by CDL)

On the morning of November 1, 2021, we (CDL, JG, and PR) performed an inspection of the (b) (4) Production facilities. The inspection began in the receiving area of the warehouse, which is comprised of (b) (4) truck bays for deliveries. All materials received here are verified against packing lists, visually inspected, and entered into

(b) (4) Materials that pass visual inspection are also affixed with a yellow (quarantined) label and further inspected by QI personnel. According to the firm, (b) (4) (also referred to as starting material (SM)) for pDNA production are received from Moderna, (b) (4) pending pickup by Incoming Quality Assurance (IQA). (b) (4) we asked for a list of personnel with access to the QI and warehouse areas. The lists provided by the firm confirmed that (b) (4) people (including the (b) (4) Department) had access to the QI area, while (b) (4) people (including (b) (4) department personnel) had access to the warehouse. We noted that access to the (b) (4) should be limited to ensure secure storage of this SM. For additional information regarding secure storage of (b) (4) see the General Discussions with Management section of this report (Item No. 6 – Inspector Lynch).

The walk-through continued in the staging area for production materials (Room (b) (4) It was noted that the staged materials included (b) (4) The firm acknowledged that they currently utilize (b) (4) (b) (4) Upstream activities (b) (4) (b) (4) for Moderna pDNA are (b) (4) (b) (4) while downstream activities (b) (4) are (b) (4) Production facilities each house (b) (4) however, to date, (b) (4) activities for Moderna pDNA lots have (b) (4) The firm acknowledged that a dedicated production area (b) (4) Moderna (b) (4) Production facility (b) (4) For more information regarding (b) (4) see the General Discussion with Management section of this report (Item No. 4 – Inspector Lynch).

(b) (4)

(b) (4) Air handling units (AHUs) for the production areas are housed in (b) (4) floor mechanical area.

The inspection then proceeded to the (b) (4) floor of this facility houses a mechanical area, several QC laboratories, (b) (4) separate offices areas, and the ASDS area. Within ASDS (Room (b) (4) we noted a number of (b) (4) The firm indicated that all final (b) (4) of Moderna pDNA are stored in this room prior to shipment. The firm also confirmed that no stability studies are performed onsite for Moderna lots.

The firm utilizes a paper-based system to track samples/final product containers in ASDS; however, when we asked to see the current inventory of (b) (4) Moderna pDNA lots, ASDS staff members were unable to immediately locate the bio-reconciliation forms for these lots. Review of some active bio-reconciliation forms for other products revealed that these forms appear to capture all appropriate information; however, it was unclear how they are tracked or controlled. (b) (6), (b) (7)(C) noted that printouts of these forms can be tracked (which was confirmed in subsequent discussions with the firm). The firm also indicated that (b) (4) been purchased (b) (4) the tracking and control of final product (b) (4) in CY2022. Regarding physical storage of Moderna pDNA (b) (4) the firm acknowledged that they do not maintain a dedicated (b) (4) shelf/bin for storage of these lots; however, after some searching, ASDS staff members were able to locate a pDNA lot (No. (b) (4) Given the delay in locating the forms and physical location of the (b) (4) final containers, it was recommended that the firm establish a dedicated and labeled shelf/bin (or unit) for storage of the Moderna pDNA construct. For additional information regarding the controlled issuance of documentation and storage/tracking of the (b) (4) see the General Discussions with Management section of this report (Item Nos. 3 and 7 – Inspector Lynch).

QC activities are performed in Room Nos. (b) (4) (b) (4) Moderna pDNA).

Shipping activities are performed in Room (b) (4) (also located on the (b) (4) floor (b) (4) Production facility). After Moderna requests that final material be shipped (via completion of a shipping specification form), packaging is performed in ASDS with oversight by Operational Quality Assurance (OQA). OQA then accompanies the packaged material to Room (b) (4) where it is shipped in accordance with the signed shipping specification form.

## Quality System

(Written by CDL)

The Aldevron QMS was designed as a system of interrelated processes with four core functions: QA; QC; Regulatory and Compliance; and Continuous Improvement. The main activities associated with the QMS are defined as Quality System Processes (QSPs) and are grouped in the following six categories:

- *Regulatory and Customer Requirements*
- *Product Realization*
- *Measurement, Analysis, and Improvement*
- *Management Responsibility*
- *Resource Management*
- *Continual Improvement*

Per the opening presentation, the firm's approach to Quality is also based on the following:

- Risk based approach based on ICH Q9, ICH Q10, and regulatory intelligence (Guidance documents, industry trends, 483 Observations, Warning Letters, etc.)
- Understanding of domestic and international requirements (CFR vs. EudraLex)
- Leveraging of technology:
  - (b) (4) installed as the new electronic Quality Management System (eQMS) in August 2020
    - Allowed the firm to convert their QE, CAPA, and Change Control procedures from paper-based to electronic
  - Transition from (b) (4) for better material control (with an improved system interface and communication)
  - (b) (4) purchased and slated for installation (b) (4) (b) (4)
- Creation of an environment for continuous process improvement
  - Optimization of various processes
  - Utilization of human error reduction (HER) principles
  - Initiation of (b) (4) events as part of the Quality culture
  - Root cause analysis tools
    - Develop and implement robust CAPAs
    - Reduce the number and severity of nonconformances and QEs.
- Maintain permanent inspection readiness status
  - Part of Quality and Regulatory intelligence
  - Utilization of mock inspections and client audits
  - Address all feedback from internal and external sources

*Expanded Overview of the QMS*

(Written by CDL)

On November 2, 2021, an expanded overview of the firm's QMS was provided by (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) During the presentation, (b) (6), (b) (7)(C) confirmed that a number of enhancements had been made to the firm's QMS in the past 12 months. These enhancements included reorganization of the Quality Unit and installation of a new Quality Leadership Team (QLT) through an infusion of industry quality talent in the "latter portion of 2020." A retrospective and comprehensive assessment was also performed for all QMS elements sitewide. Additionally, a (b) (4) Quality event was performed in November 2020 to enhance the QE process while the comprehensive assessment was being conducted. (b) (6), (b) (7)(C) noted that one of the first enhancements to the QE process was transfer of planned deviations into the temporary change control process.

Following the retrospective assessment of the QMS, the QE investigation process was revised to include the following requirements:

- A cross-functional team must be assembled
- Interviews must be conducted
- All relevant records must be reviewed
- All information related to the event must be collected and summarized
- Each event must be classified as follows:
    - Level 1 – Minor – no potential impact to patient safety or product quality, purity, identity, efficacy, or safety (no CAPA required)
    - Level 2 – Major – requires an investigation or comprehensive analysis of existing data to determine the potential impact to patient safety and/or impact to product quality, purity, identity, efficacy, or safety (CAPA required)
    - Level 3 – Critical – impact to patient safety and/or product quality, purity, integrity, efficacy, or safety is immediately evident. A critical QE is a significant event and any impacted product has a high probability of rejection. (CAPA required)
- Each investigation must be scoped correctly as it may impact other lots or processes
- Root cause analysis tool must be utilized to identify the true root cause (immediate vs. long-term)
- All investigations must be completed within (b) (4) however, more intensive investigations may be extended (b) (4)
- All OOS investigations must be performed in accordance with FDA's "Guidance for Industry: Investigation Out of Specification (OOS) Test Results for Pharmaceutical Production" (October 2006)

Operations and Quality Leadership were trained on the new QE procedure (SOP-QA-0023 – Quality Event (QE) Investigation and Report) in December 2020. The SOP was subsequently designated as effective in January 2021.

The firm also reported that the definitions and electronic workflows for QEs, CAPAs and effectiveness checks (ECs), and change controls were optimized in (b) (4) (effective May/June 2021). Regarding CAPAs and ECs, the firm acknowledged that the optimized process has improved control of new CAPAs/ECs and helped facilitate closure of outstanding paper-based CAPAs. The firm also confirmed that the change control process was revised to include more prescriptive requirements.

The following metrics, monitoring, and process controls were also implemented in the last 12 months:

(b) (4) QE meetings (initiated in March 2021)

(b) (4)

- (b) (4) Quality Reviews

During the expanded QMS presentation, a number of QE clusters were also discussed. The firm acknowledged that these events had continued after implementation of the revised QE process and were still being monitored and assessed. The identified clusters are as follows:

- Misclassification of events
- Overuse of Human Error as root cause for an event
- Insufficient documentation regarding identification of (b) (4) as an in-house isolate
- EM events trending; many investigations did not include corrective actions
- Improper (b) (4) cleaning and sanitization

I reviewed the remediation activities (e.g., CAPAs, investigation addendums based on revised QE procedures, internal and external trainings, etc.) associated with these cluster events and noted no deficiencies. Regarding the recent enhancements to the QMS, a number of discussions were held to evaluate the organizational and systemic changes described above. For additional information regarding these discussions, see the General Discussions with Management section of this report (Item No. 2 – Inspector Lynch).

*Quality Events and CAPA Management*

(Written by CDL)

As noted above, the firm's QE procedures are outlined in SOP-QA-0023 – "Quality Event (QE) Investigations and Report". In brief, QEs are defined as: (1) any unplanned nonconforming event; (2) noncompliance with company standards such as Policies, SOPs, Work Instructions, Methods; or (3) failure to comply with GxP expectations. As these events may have a negative impact on the quality, purity, identity, efficacy, or safety (QPIES) of any product they must be investigated. Every nonconformance starts as QE and is then designated with one of the following classifications: (1) OOS; (2) supplier corrective action report (SCAR); or (3) it remains as a QE. At the start of an investigation, each confirmed nonconformance event is designated as a QE until an initial classification code (minor/major/critical) is assigned based on the severity of the event, the scope of the investigation, and the realized or potential impact to product quality or patient safety. After the QE has been comprehensively investigated (and slated for closure), the initial categorization is revisited and may be adjusted (as necessary) to accurately reflect the severity and scope of the investigation. Quality is responsible for ensuring that the completed investigation is appropriately categorized and scoped (to include all potentially impacted lots or processes).

The firm's CAPA procedures are outlined in a stand-alone document (SOP-QS-0018 – "CAPA Program") and referenced in the QE SOP. As noted above, CAPAs are required for (b) (4) QEs. Completion timelines for CAPAs are commensurate with the event and the scope of the CAPA (and associated tasks to be implemented), while the timing of effectiveness checks is dependent on the number of process cycles (or occurrences for less frequent activities) for the activity which precipitated the need for a CAPA. CAPA due dates may be extended with appropriate justification and QA approval; second extensions may also be requested via the same requirements and escalation to a site Quality Director (or designee). Of note, the firm's expanded QMS presentation indicated that CAPAs may be extended (b) (4) times; however, SOP-QS-0018, is somewhat contradictory in that it states that "if the CAPA has not been completed after (b) (4) the Quality Director must be informed, and further action determined prior to any further extension approvals." CAPAs are considered complete after all tasks have been implemented and approved by Quality. Following Quality approval of an effectiveness check, the associated CAPA is considered closed.

During the inspection, I reviewed a number of QEs and CAPAs for activities associated with production of pDNA for Moderna. In general, the investigations associated with these events appeared to become more comprehensive in conjunction with the revised QE procedure, implementation of optimized workflows in (b) (4) and completion of various training activities. The scope and appropriateness of CAPA tasks (and implementation) also appeared to improve in conjunction with the above noted QMS enhancements.

*Quality Events*

(Written by PR)

I reviewed the firms current Quality Event SOP and a list of approximately 68 QEs since September 2020 (**see Exhibit PR17**). The majority of QEs were classified as Level 1; five Level 2 QEs, and no Level 3 (Critical) QEs (**see Exhibit PR17**). The list of QEs included EM action level excursion investigation and Out of Specifications (OOS) QEs (5 total, **see Exhibit PR19, page 3-5**), which were also reviewed.

Quality Events (QEs) and associated CAPAs were reviewed for thoroughness, completeness, and appropriate follow-up. I also reviewed SOP-Q5-0018, "CAPA Program" and six CAPAs that were initiated since September 2020 and noted no deficiencies.

I discussed a series of mold events that are included in a summary presentation in **Exhibit PR15**. Details regarding these discussions can be found in the General Discussion with Management section of this report (Item No. 1 – Investigator Raju).

*Change Control*

(Written by PR)

I reviewed the Change Control SOP and a list of Moderna product specific change controls since January 1, 2021. I recommended that they report major and critical changes to the license holder. (b) (6), (b) (7)(C) stated all major and critical changes are reported to the license holder.

*BPDRs*

(Written by PR)

Moderna submits all BPDRs and (b) (4) Quality Events at Aldevron are reported to Moderna per their Quality Agreement.

*Quality Audits*

(Written by PR)

I reviewed SOP-QS-0011, "Quality Audits", the firm's internal audit schedule, and Aldevron's Mock QC Audit Report Findings, and I noted that internal audits were performed per Aldevron's established schedule. No concerns were noted.

*Document Control/Document Storage*

(Written by CDL)

The firm utilizes a hybrid approach for document management. This approach is comprised of an electronic system (eQMS/(b) (4) that houses a combination of original electronic records and paper records. Each record must follow the Attributable, Legible, Contemporaneous, Original, and Accurate (ALCOA) principles for lifecycle of the document. All paper-based documents are stored (b) (4) within the Fargo facility. Archived documents are stored offsite at (b) (4) (b) (4)

*Product Release*

(Written by CDL)

I discussed the firm's product release procedures with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) This process begins with QA review of production records and test results in accordance with SOP-QA-0013 – "Quality Assurance Review of Manufacturing and Test Records." A Certificate of Analysis (CoA) is then generated in accordance with SOP-QC-0034, "Certificate of Analysis" and reviewed by QA. Materials that meet all release criteria are then approved by QA and released within the

(b) (4) system. Regarding release of (b) (4) lots, (b) (6), (b) (7)(C) noted that a review package is prepared for each lot to include: (1) executed batch records; (2) a list of QEs (major and critical), CAPAs, change controls, etc.; and (3) a CoA. Certificates of Compliance (CoC) and manufacturing summaries may also be included if requested by Moderna. The review package is then forwarded to Moderna for review. Although (b) (4) (b) (4) lots are considered released at this point, final containers are maintained at Aldevron (within ASDS) until a shipment specification form is received from Moderna.

**Production System**

*Production Operations Observed*

(Written by CDL)

- **Upstream Activities for Lot No.** (b) (4) – on November 2, 2021, we (CDL, JG, and PR) observed upstream activities (b) (4)
(b) (4)
(b) (4) The firm acknowledged our comments and noted that the (b) (4)
(b) (4)
(b) (4) For more information regarding these discussions, see the General Discussions with Management section of this report (Item No. 1 – Inspector Lynch).

- **Downstream Activities for Lot No.** (b) (4) – on November 3, 2021, we (CDL, JG, and PR) observed downstream activities (b) (4)

(b) (4) The firm explained that after the (b) (4)

- (b) (4) **Activities for Lot No.** (b) (4) – on November 5, 2021, we (CDL and JG) observed the (b) (4) These activities were conducted (b) (4)

(b) (4) *Process Validation for* (b) (4)

(Written by CDL)

The firm's governing policies for validation of (b) (4) processes are outlined in (b) (4) (b) (4) The firm utilizes a (b) (4) approach for (b) (4) that are deemed to be the greatest challenge to the process and/or the greatest risk of (b) (4) For the (b) (4) the firm utilizes the following parameters as the worst-case scenario for (b) (4) conducted with (b) (4) (b) (4) The rationale behind the preceding parameters was attributed to the (b) (4) The firm also acknowledged that while (b) (4) (b) (4) are performed to provide the highest level of assurance that the pDNA is (b) (4) (and to ensure patient safety and product quality), though the resultant pDNA is (b) (4) (b) (4)

During the inspection, I reviewed the initial and the most recent (b) (4) reports for the (b) (4) (b) (4) (b) (4) Results showed that each (b) (4) met study requirements.

*Batch Records*

(Written by CDL)

Master batch records (MBRs) were reviewed for Lot Nos. (b) (4) (b) (4) Both MBRs appeared to contain detailed instructions with numerous steps that require verification by (b) (4) No deficiencies were noted with the firm's MBRs.

*Changeover Procedures*

(Written by CDL)

SOP-GMP-0061, "GMP Change Over" governs the firm's procedures for production room changeovers and release of manufacturing rooms. I reviewed this SOP and noted that it contained appropriate sections (and procedures) for cleaning of bidirectional personnel and materials flow processing rooms, (b) (4) cleaning (performed every (b) (4) or as necessary based on investigations or EM trends), cleaning of (b) (4) flow processing rooms, and (b) (4) (utilizing Form (b) (4) (b) (4) pending QA review and release. All executed changeover steps are documented on form FR-GMP-GRN-0013 – Change Over Checklist.

I also reviewed SOP-GMP-065, "ISO (b) (4) Cleanroom Cleaning", which outlines the cleaning procedures for the various cleanroom suites (b) (4) (b) (4) suites). The firm utilizes (b) (4) cleaning reagent (b) (4) (b) (4) to clean these suites. Cleaning events are captured via a checklist (FR-GMP-GEN-025) (b) (4) clearance, deep cleaning (performed every (b) (4) changeover cleaning, (b) (4) cleaning, surface cleaning of benchtops, chairs, and other equipment, passthrough cleaning, wall cleaning, floor cleaning, and gowning area wall/floor cleaning (performed (b) (4) The SOP appeared to contain appropriate steps for order of operations (cleaning (b) (4) (b) (4) frequency of cleaning, and (b) (4) for (b) (4) cleaning reagent.

Changeover and cleaning records were reviewed and found to be satisfactory.

*Disinfectant Efficacy Studies*

(Written by CDL)

I reviewed the following the documents associated with the firm's disinfectant validation program:

- VAL-2586 – VP-041 – "Disinfectant Validation Master Plan for Aldevron GMP Manufacturing Operations"

  This document outlines the overall approach of the disinfectant validation program as well as the development of strategies for validating additional disinfectants, validating disinfectants on newly identified surfaces, and validating current disinfectant procedures on environmental isolates. Validation of disinfectants is evaluated (b) (4) by a cross-functional team that includes Manufacturing, Facilities, and Quality Environmental Control. The cross-functional team analyzes data to identify any potential gaps in the firm's cleaning and disinfection program and then designs a study utilizing a risk-based approach. If a surface, disinfectant, and organism combination has been previously studied, it is not re-tested as the results of the studies are considered to be cumulative. To date, the firm has validated (b) (4) disinfectants for use on all applicable and compatible surfaces: (b) (4) evaluated in the 2020 study); (b) (4) evaluated in the 2021 study).

- VAL-1285 – "Final Summary Report for Disinfectant Efficacy Testing for Multiple Surfaces 2020"

  Results from this 2020 study showed that (b) (4) met specifications for reduction of microorganisms on (b) (4) material/surfaces, (b) (4) (b) (4) One deviation initiated during this study was reviewed and found to be appropriately resolved.

- VAL-1597 – Validation Plan for 2021 Disinfectant Effectiveness Testing

  This protocol was developed for testing of (b) (4) microorganisms (based on EM data) that were not represented in the 2020 study: (b) (4) (b) (4) Although this study was not complete at the time of the inspection, I was able to view the interim report from PPD (dated October 8, 2021). Results showed that (b) (4) met all acceptance criteria at designated (b) (4) for all of the above noted surfaces and (b) (4) Results from testing of (b) (4)

were pending at the time of the current inspection. No deviations were initiated during the testing summarized in the interim report.

Results from the preceding studies appear to indicate that the disinfectants utilized by the firm in their Fargo manufacturing areas are adequately validated for use in accordance with established procedures.

*Gowning Practices*

(Written by PR)

I reviewed SOP GMP-0066, "ISO (b) (4) Cleanroom Gowning Procedure"; SOP-GMP-0060, "Facility Gowning" and SOP-GMP-0129, "Aseptic Practices and Cleanroom Behaviors".

I also observed gowning practices in the ISO (b) (4) Building Room (b) (4) We all observed that changing to (b) (4) gowning from (b) (4) gowning occurred within a (b) (4) area that was (b) (4) from the room by (b) (4) were about to be initiated (b) (4) we noted that the gowning procedures did not appear to be best practice for this area. For more information regarding our concerns with the gowning procedures in Room (b) (4) see the General Discussions with Management section of this report (Item No. 1 – Inspector Lynch).

*Production System Coverage (PR)*

My coverage of production included but was not limited to a review of the pDNA manufacturing process, manufacturing procedures, flow diagrams (**see Exhibits PR4 & PR5**), and batch records. A listing of upstream production SOPs, Downstream Production SOPs, and (b) (4) Production SOPs, is included in **Exhibit PR8**. A listing of Moderna (b) (4) Master Batch Records is included in **Exhibit PR9**. My review noted no deficiencies.

**Facilities and Equipment System**

*Environmental Monitoring Controls/Action Levels*

(Written by PR)

I reviewed EM specifications in SOP QC-0108 (**see Exhibit PR16, page 2**), and I was concerned that the ISO (b) (4) action level for fungus/mold was too high and not based on operation of the facility. (b) (6), (b) (7)(C) said they had not had an action level excursion in the ISO (b) (4) areas but he understood my concern and presented me with updated levels which appeared acceptable. Refer to the Discussion with Management section for more details. Environmental monitoring sample locations and frequency were evaluated, and

SOP-QC-0171, "Quality Control Water Monitoring", was also reviewed and found acceptable.

*Heating, Ventilation, and Air Conditioning (HVAC)*

(Written by CDL)

The (b) (4) Production facilities each house a master air handling unit (AHU) that supplies make up air to the nine AHUs located across the site. The (b) (4) pDNA (b) (4) suites are designed as (b) (4) rooms, while other areas utilize (b) (4) (b) (4) air (b) (4) air. Air that supplies the production areas goes through (b) (4) before being (b) (4) HEPA filtration unit. Pressure differentials in the production areas are (b) (4) in conformance with ISO 14644. As the HVAC system is (b) (4) unit, it was designed to deliver the required number of room exchanges in each area based on room classification. Review of procedures and tasks associated with the HVAC system noted no deficiencies.

*Environmental Monitoring Performance Qualifications*

(Written by CDL)

I reviewed the following environmental monitoring performance qualification (EMPQ) reports associated with (b) (4) which service the main production areas:

- VAL-2613 – "Final Summary Report for PQ-1345, PQ-1354, PQ-1367, and PQ-1368, EMPQ of the Rooms Served by (b) (4)

  The scope of this EMPQ was limited to the non-viable and viable particulate and surface sampling and testing of specified rooms (served by (b) (4) in the (b) (4) Production facility under static and dynamic conditions (b) (4) cleaning of the area. Sampled and tested rooms include the following:

  (b) (4)

  Results showed that all (b) (4) plates), and (b) (4) plate samples met pre-defined acceptance criteria. Based on these results, the rooms were released as suitable for manufacturing activities.

- FSR_MT_229 – "Final Summary Report for PQ-581, EMPQ of the (b) (4) Static Viable Particulate of the (b) (4) and (b) (4) Served by (b) (4)

  The scope of this EMPQ was limited to the (b) (4) viable particulate sampling and testing of rooms associated with the (b) (4) areas served by (b) (4) (b) (4) in the (b) (4) Production facility under static conditions (b) (4) cleaning of the area. Sampled and tested rooms include the following:

  (b) (4)

  Results demonstrated that all (b) (4) plates), and (b) (4) plate samples met pre-defined acceptance criteria. Based on these results, the rooms were released as suitable for manufacturing activities.

*Facility Cleaning and Sanitization*

(Written by CDL)

Facility cleaning procedures and logs were reviewed in conjunction with assessment of the firm's changeover procedures. No deficiencies were noted.

*Water Systems*

(Written by CDL)

The firm currently utilizes (b) (4) WFI for (b) (4) activities. Each (b) (4) is reviewed before release for manufacturing use. The firm also indicated that qualification of (b) (4) was ongoing.

A purified water (PW) system is utilized for preparation of (b) (4)

*Critical Computerized Systems*

(Written by PR)

Critical computerized systems (CCS) are described in the Site Master File in Section 4.2.3. All critical computerized systems at the site undergo a strict validation process to ensure the system meets predetermined specifications and all requirements outlined in 21CFRPart11. I reviewed the most recent Software System Inventory Report, VAL-0512, reviewed audit trails in batch records, and document conformance to ALCOA standards. I also reviewed SOP-FE-0002, "Aldevron Event Response and Recovery", which covered responses to BMS Alarms and noted no concerns.

*Pest Control*

(Written by PR)

Integrated Pest Management is conducted per SOP-FE-0007. Section 3.2.3 includes a requirement to report any observed pests or evidence of pests (such as droppings) in the manufacturing areas to the Quality Assurance and Facilities Departments. I reviewed the pest control program with (b) (6), (b) (7)(C) and no concerns were noted. I also reviewed the Quality Event listing and noted no Quality Event for pest sightings.

*Major Equipment Qualifications*

(Written by CDL)

A table of product contact equipment and materials for manufacture of (b) (4) was submitted to the BLA in Section 3.2.A.1.3 (Material Equipment and Contamination Control). Review of this table revealed that the bulk of the equipment and product contact items utilized in the (b) (4) manufacturing process are (b) (4) (b) (4) Dedicated product-contact equipment items include (b) (4) (b) (4) It was also confirmed that no shared product contact equipment items are utilized in the production of (b) (4) A table of non-product contact/re-usable equipment was also provided in Section 3.2.A.1.3 and included items such as (b) (4) During the inspection, I reviewed the Installation and Operational Qualification (IQ/OQ) reports for the following pieces of equipment:

(b) (4)

Results showed that all IQ/OQ tests for the preceding equipment met acceptance criteria and all were released for their intended use.

*Equipment Cleaning*

(Written by CDL)

As noted above, the bulk of the manufacturing equipment and product contact items used to prepare (b) (4) However, the firm does have general cleaning procedures in place for stationary equipment (b) (4) and mobile equipment (b) (4) These procedures consist of the following steps:

(b) (4)

During the inspection, I reviewed VP-011- "Cleaning Validation Master Plan for Aldevron GMP Manufacturing Operations". As the firm maintains (b) (4) (b) (4) I also reviewed VAL-1452 – "Final Summary Report for PQ-930 Cleaning Validation Performance Qualification Protocol for (b) (4) (b) (4) This study challenged the effectiveness of the (b) (4) (b) (4)

As part of my coverage of the equipment cleaning program, I also reviewed the following SOPs:

- SOP-GMP-0059 – "Work Surface Equipment Cleaning" – this procedure outlines the steps for cleaning work and equipment surfaces within (b) (4) production rooms and (b) (4) rooms before and after use. Level 1 cleanings are performed on (b) (4) while Level 2 cleanings are performed to (b) (4)
- SOP-QC-0173 – "Cleaning QC Incubators"
- SOP-GMP-0086 – "Use and Maintenance of (b) (4) (b) (4)
- SOP-GMP-0074 – "Use and Maintenance of (b) (4)

Equipment use and maintenance logs (Form FR-FE-0028; Revision 01) were also reviewed for Room (b) (4) Room (b) (4) These forms appeared to capture the required information in accordance with the above noted procedures.

No objectionable conditions were noted with the firm's general cleaning program or procedures.

**Materials System**

*Supplier Qualification*

(Written by PR)

I reviewed the SOP-QE-0008, "Evaluating Supplier Qualification", the current Approved Supplier List, and related Supplier Self-Assessment and Supplier Information Forms. The SOP for Supplier Performance Assessment, SOP-QS-0017 and SOP-QS-0004, "Conducting Supplier Audits" and SOP-QS-0022, (b) (4) Supplier Management. A listing of Moderna product on site is included in **Exhibit PR14** and included (b) (4) lots of (b) (4)

All incoming materials are received into Aldevron in a "quarantined status". Critical raw materials are processed through the initial receiving bay where visual inspection is conducted by qualified personnel. Materials that pass initial inspection are assigned and labeled with a unique Aldevron Lot Number (ALN) that correlates to the Aldevron Material Number (AMN). The ALN allows the material to be traceable via Aldevron's Raw Material Management System (RMMS). The AMN defines the parameters of the acceptance criteria (e.g., certificate of analysis) for raw materials. If material fails inspection in the receiving bay, the material will be handled one of three ways: labeled for research grade only use, returned to the manufacturer, or disposed. All materials

that pass initial inspection will be sent to incoming quality inspections where a thorough inspection of the material will occur.

All raw materials that are processed through receiving are then inspected by Quality Inspections personnel. The Quality Inspector will enter the materials manufacturer lot number and expiration date into the RMMS. In addition, all acceptance criteria will be uploaded to the RMMS and will be retained for review. The inspection process consists of verifying the materials information against the Aldevron general inspection record and applicable certificates. Once the general inspection has been completed the materials information will be verified by a final quality review and marked for approval as applicable. After a successful inspection, the material is converted from a "quarantine status" to a "released status" and only Quality can effectuate that change in status.

*Receipt and Storage of Incoming Material*

(Written by PR)

I reviewed SOP-QI-0003, "Receipt and Storage of Incoming Material", which was the procedure for receipt and storage of manufacturing materials, and example receipt packages for pDNA (b) (4) I also observed Warehousing and Quality Inspection (QI) operations on November 1 & 3, 2021.

We reviewed the Warehouse Access List and the Quality Inspection Access List, which also sufficed for access to storage units that contained (b) (4) of pDNA (Moderna (b) (4) (b) (4) We addressed our concern that > (b) (4) people had access to both the Warehouse and QI areas (lack of restricted access).

## Packaging and Labeling System

*Packaging and Shipping Procedure*

(Written by PR)

Packaging & Shipping pDNA for COVID-19 vaccine did not take place during the inspection. I reviewed the shipping SOP-SR-0010, Shipping Final Material and observed a mock overview of shipping in the (b) (4) Production Areas on November 1, 2021. (b) (4) Labeling is conducted by (b) (4) in the (b) (4) production area. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) said that (b) (4) labeling of pDNA (b) (4) and packaging of pDNA (b) (4) and shipment occurs (b) (4) I observed the storage of (b) (4) of Moderna's pDNA in (b) (4) (**see Exhibit PR14**).

I observed a simulated printing of the (b) (4) label and also reviewed SOP-GMP-0035, Label Printing and Reconciliation. No deficiencies were noted.

**Laboratory Control System**

(Written by PR)

Laboratory system coverage included but is not limited to overview of laboratory operations, plasmid material specifications (**see Exhibit PR10**), in-process release criteria (**see Exhibit PR11**), a review of analytical methods (**see listing in Exhibit PR19**), a listing of OOSs (**see Exhibit PR19, page 3-5**). I did a walk-through of laboratory operations on November 4, 2021.

Laboratory methods that I reviewed pertained to plasmid DNA and revealed no concerns.

## OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

No inspectional observations were issued at the conclusion of the inspection; however, a closeout meeting was conducted to review the discussion items and recommendations outlined below.

## GENERAL DISCUSSIONS WITH MANAGEMENT

(Written by CDL/PR)

*Discussion Items – Inspector Lynch*

- ***Item No. 1 – Gowning Procedures and Background Environments for Execution of Certain Upstream Activities***

  During observation of upstream activities (b) (4) (b) (4) Room (b) (4) (ISO (b) (4) it was noted that operators performing the various setup and support activities were outfitted with (b) (4) Following completion of these activities, (b) (4) of the operators gathered new cleanroom gowning and changed into the elevated gowning materials in a (b) (4) area near the door (with (b) (4) on the floor). The remaining (b) (4) operators also donned their sterile gowning materials in the same manner. As (b) (4) was not available for gowning and the operators (b) (4) the (b) (4) several times (while also being around lesser gowned operators), we noted that the gowning procedures did not appear to be best practice given (b) (4) that were about to be executed (b) (4) in this room. It was also noted that the current version of SOP-GMP-0066 – "ISO (b) (4) Cleanroom Gowning Procedure" (Revision 03), had been updated recently (October 27, 2021) to include Section 6.5 (Gowning Procedures for (b) (4) Operations Conducted in ISO Class (b) (4) Production Rooms),

thereby suggesting that the operators may have been inexperienced with a new gowning process that did not appear to be optimized (or best practice) for this area.

Regarding execution of certain upstream activities, it was noted that SOP-GMP-0066 defines ISO (b) (4) operations (b) (4) (b) (4) operations conducted in an ISO (b) (4) classified (b) (4) Review of the lot location summary for (b) (4) confirmed that (b) (4) (b) (4) activities for all preceding lots had been conducted in (b) (4) Production facility Room (b) (4) classified environments); however, it was unclear why the firm decided to utilize Room (b) (4) Lot No. (b) (4) Furthermore, as Room (b) (4) (b) (4) we also noted that (b) (4) utilized for these steps are typically (b) (4) (b) (4)

The firm acknowledged that there was no reason as to why they (b) (4) (b) (4) utilized in Room (b) (4) The firm did note that (b) (4) Production facility room (b) (4)

Regarding our gowning concerns, the firm's initial response was that the current procedure was not an issue as long as operators did not crowd the gowning (b) (4) However, the firm ultimately revised SOP-GMP-0066 (Revision 04, dated November 4, 2021) to include enhanced instructions (Section 6.5) for conducting certain upstream operations: (b) (4) (b) (4) Gowning procedures in the ISO (b) (4) area were also revised to (b) (4) We also recommended that the firm consider best practices for gowning, room classification, and (b) (4) of certain upstream activities (e.g., (b) (4) Moderna products in the (b) (4) Production facility. (b) (4), (b) (5), (b) (7)(E) (b) (4), (b) (5), (b) (7)(E) (b) (4), (b) (5), (b) (7)(E)

- ***Item No. 2 – QMS Enhancements***

As noted above, a number of organizational and systemic changes were made to enhance the firm's QMS. I noted that while these changes appeared to be appropriate improvements to the QMS, the sheer number and recent implementation of many of the enhancements dictates that more time is needed before an accurate assessment can be made regarding their effectiveness. (b) (5), (b) (7)(E)

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

- ***Item No. 3 – Controlled Issuance of Documents and Forms***

  During the inspection walk-through of ASDS, it was noted that the firm utilizes a paper-based system for tracking samples and final containers. As we expressed some concern with the controlled issuance and tracking of the bio-reconciliation forms utilized in ASDS, the firm decided to take a holistic approach in evaluating their document control system. Specifically, (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) confirmed that the approval step for a recent update to SOP-QS-0006- "Document Issuance and Reconciliation" was halted so the firm could discuss addition of language that requires all documents and forms to be printed by QA. (b) (5), (b) (7)(E) (b) (5), (b) (7)(E)

- ***Item No. 4 – Dedicated Production Area for Moderna Products***

  (b) (6), (b) (7)(C) (b) (4) (b) (4) (b) (6), (b) (7)(C) also noted that the (b) (4) The firm was reminded that a (b) (4)

- ***Item No. 5 – Installation of*** (b) (4)

  As noted above, the firm purchased (b) (4) tracking of final container samples in ASDS. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) confirmed that he decided to delay installation of this (b) (4) (b) (4) the firm was focused on preparations for this inspection. The firm estimated that the new (b) (4) would be installed in (b) (4) (b) (4), (b) (5), (b) (7)(E) (b) (4), (b) (5), (b) (7)(E)

- ***Item No. 6 – Security and Access to QI and Warehouse*** (b) (4)

  During our walk-through inspection on November 1, 2021, it was noted that the QI and warehouse (b) (4) utilized for storage of (b) (4) As many people have access to these areas (b) (4) we noted that security measures should be implemented to limit access to the (b) (4) The firm acknowledged our comments and (b) (4) The firm indicated that the (b) (4) (b) (4) SOP-QI-003 – "Receipt and Storage of Incoming Material." During our

observation of VI inspection activities for SM on November 3, 2021, we did confirm that (b) (4)

- ***Item No. 7 – Dedicated Storage Area for*** (b) (4) ***Final Containers***

As noted above, our walk-through inspection of ASDS revealed that the firm did not have a dedicated shelf/bin/(b) (4) for storage of (b) (4) final containers (b) (4) (b) (4) Given the need for tracking and control of this (b) (4) starting material, we recommended that they establish a dedicated shelf/bin or (b) (4) (if possible) for storage of final containers. During the opening meeting on November 3, 2021, the firm confirmed that (b) (4) would be dedicated for storage of (b) (4) (b) (4) final containers in ASDS.

*Discussion Items – Investigator Raju*

- ***Item No. 1 – Mold Excursions***

Mold excursions in (b) (4) from August 2020 – August 2021 could have been investigated more thoroughly. I reviewed a trend of QEs that had to do with fungal excursions (b) (4) species) in the Room (b) (4) Production Area (**see Exhibit PR15, page 2**). The QEs are included in **Exhibits PR24-PR32**. (b) (4) operations occur in the (b) (4) (**see Exhibit PR7, page 2**), where the (b) (4) (b) (4) (**see Exhibits PR4 & PR5**). Quality Event (Issue-2020-0048) occurred on September 16, 2020, a viable airborne species was identified (fungal (b) (4) (**see Exhibit PR27, page 10**) and CAPA-2020-0021 (**see Exhibit PR28**) was initiated. On May 19, 2021, in Room (b) (4) a viable surface sample (fungal (b) (4) was detected in (b) (4) which led to the initiation of QE-2021-0300 (**see Exhibit PR29, page 2**). Since QE-2021-0300 was initiated due to the presence of fungal (b) (4) (b) (6), (b) (7)(C) stated that the corrective actions specified in CAPA-2020-0021 were ineffective (**see Exhibit PR28, page 14**). A new CAPA was not initiated in response to QE-2021-0300 and I told (b) (6), (b) (7)(C) that one probably should have been initiated. On August 1, 2021, and August 23, 2021, fungal species (b) (4) were again detected in Room (b) (4) QE-2021-0455 (**see Exhibit PR30**) and QE-2021-0476 (**see Exhibit PR31**) were respectively initiated (**see Exhibit PR15, page 2**). CAPA 2021-0146 was initiated (**see Exhibit PR32**), and an existing open CAPA 2021-0061 (**see Exhibit PR26**) was included as an additional corrective action.

During the closeout meeting on November 5, 2021, I mentioned that CAPA #24642, dated August 6, 2020, involved corrections to Room (b) (4) fungal excursions and had occurred before the first Quality Event (ISSUE, 2020-048) listed in **Exhibit PR15**, page two. (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C), (b) (6), (b) (7)(C) said the there was a (b) (4) in Room (b) (4) Product Area, and they were recently (b) (4) and

they have had no fungal recoveries since the (b) (4) was also implemented as a part of the cleaning/disinfection program for the Room (b) (4) (b) (4) (**see Exhibit PR26, page 5**). CAPA 2021-0146, Titled: "(b) (4) cleaning (b) (4), dated September 1, 2021, was initiated (**see Exhibit PR32, page 1**), but has not been completed, and would (b) (4) cleaning (b) (4) in Room (b) (4) I explained that since these corrective actions were recently implemented, I could not evaluate the impact of the corrections, (b) (5), (b) (7)(E)

I explained that it was too early to assess the effectiveness of their corrective actions and explained that it was a year between the first fungal excursion in Room (b) (4) August 6, 2020 (**see Exhibit PR24**), and the last one August 22, 2021 (**see Exhibit PR31**). I explained that the corrective actions that were most recently implemented, CAPA 2021-0146 (**see Exhibit PR32**), could have been implemented earlier, and in response to the first excursion.

- ***Item No. 2 – Mold Specifications***

I reviewed the ISO (b) (4) specifications for mold which are included in **Exhibit PR16, page 2**, and the active air action limit for mold was (b) (4) the surface sampling/plate action limit for mold was (b) (4) plate, and the (b) (4) plate action limit for mold was (b) (4) plate. I explained to (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) that the mold action level limits should be evaluated. (b) (6), (b) (7)(C) revised the ISO (b) (4) fungal specification limits included in **Exhibit PR16, page 2**, during the inspection and it was presented to Inspector Lynch at the conclusion of the inspection.

- ***Item No. 3 – Categorization of Quality Events***

I reviewed Quality Events (i.e., deviations) initiated since September 2020 and (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) provided a summary list included in **Exhibit PR17**. There were 53 Level 1 Minor Quality Events and 8 Level 2 Major Quality Events. I explained that some of the Level I Quality Events that I reviewed could have been potentially classified as Level 2 Quality Events. During the final closeout meeting, and even though I did not see these specific QEs, I explained that Quality Events that lead to rejected batches, environmental monitoring excursions in the ISO (b) (4) area, fungal species in any classified area, pest identification, leaks of product during production, foreign material identified in product, confirmed OOS, and any identified QE trends would potentially be categorized as Level 2 Quality Events.

**EXHIBITS COLLECTED**

(PR)

Exhibit PR1 Aldevron's Opening Presentation
Exhibit PR4 Overview of Plasmid Manufacturing Process w/in-process testing

Exhibit PR5 Manufacturing Process Flow (b) (4)

Exhibit PR6 Moderna Construct (b) (4) Lots Manufacturing since September 2020

Exhibit PR7 Aldevron Floor Diagrams (b) (4) Production Areas)

Exhibit PR8 Upstream and Downstream SOPs

Exhibit PR9 Moderna (b) (4) Master Batch Record Index

Exhibit PR10 Plasmid Material Specification, dated January 25, 2021

Exhibit PR11 Upstream In-Process Release Criteria, (b) (4) Plasmid In-Process Release Criteria

Exhibit PR14 Linear Moderna Material at Aldevron

Exhibit PR15 Summary of Fungal Excursions

Exhibit PR16 Alert and Action Level Environmental Monitoring Criteria

Exhibit PR17 Criticality Level and Totals for Quality Events

Exhibit PR18 Moderna Covid Vaccine Contract Facilities

Exhibit PR19 Description of Analytical Methods, and OOS Summaries

Exhibit PR24 CAPA #24642, dated August 6, 2020 (Fungal Excursion Routine EM Sampling of Room (b) (4)

Exhibit PR25 Trend Investigation Report QE-2021-0175 to Support CAPA-2021-0061

Exhibit PR26 CAPA-2021-0061, dated June 17, 2021

Exhibit PR27 ISSUE-2020-0048, dated September 24, 2020 (Room (b) (4) EM Fungal Excursions)

Exhibit PR28 CAPA-2020-0021, dated November 22, 2020 (Initiated in Response to ISSUE-2020-0048)

Exhibit PR29 QE-2021-0300, dated May 19, 2021 (Room (b) (4) EM Fungal Excursions)

Exhibit PR30 QE-2021-0455, August 1, 2021 (Room (b) (4) EM Fungal Excursion)

Exhibit PR31 QE-2021-0476, August 22, 2021 (Room (b) (4) EM Fungal Excursion)

Exhibit PR32 CAPA-2021-0146, dated September 1, 2021

## ATTACHMENTS

1. Form FDA 483, Notice of Inspection, issued November 1, 2021 (3 pages)

**Inspection Team:**

Christian D. Lynch – Lead Investigator
Consumer Safety Officer
CBER/OD

Jared Greenleaf
CSO, CMC/Facility Reviewer
CBER/OCBQ/DMPQ/MRBI

Prabhu Raju
CSO
ORA/OBPO/TB/Division I

**EIR Approval:**

Christian D. Lynch -S
Digitally signed by Christian D. Lynch -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300215643, cn=Christian D. Lynch -S
Date: 2022.01.27 19:01:12 -05'00'

Jared D. Greenleaf -S
Digitally signed by Jared D. Greenleaf -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003357380, cn=Jared D. Greenleaf -S
Date: 2022.01.27 17:28:48 -05'00'

Prabhu P. Raju -S
Digitally signed by Prabhu P. Raju -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Prabhu P. Raju -S, 0.9.2342.19200300.100.1.1=2000095678
Date: 2022.01.27 13:02:28 -08'00'