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CBER CMC BLA Review Memorandum

BLA STN 125752/0

SPIKEVAX (COVID-19 Vaccine, mRNA)

(b) (6)



CBER CMC BLA Review Memo, STN 125752, COVID-19 mRNA Vaccine

1. **BLA#:** STN 125752/0

2. **APPLICANT:** ModernaTX, Inc., US License Number: 2256

3. **PRODUCT NAME/PRODUCT TYPE**

SPIKEVAX (COVID-19 Vaccine, mRNA), hereafter SPIKEVAX

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

a. **Pharmacological category**

Vaccine

b. **Dosage form**

Liquid

c. **Strength/Potency**

100 mcg

d. **Route of administration**

Intramuscular

e. **Indication(s)**

Active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals
≥ 18 years of age

5. **MAJOR MILESTONES**

First Committee Meeting: September 9, 2021

Filing Meeting: September 28, 2021

Filing Action: October 27, 2021

PDUFA ADD: February 23, 2022

6. **CMC/QUALITY REVIEW TEAM**

| Reviewer/Affiliation | Section/Subject Matter |
|----------------------|------------------------|
| | All Sections |

7. **SUBMISSION(S) REVIEWED**

| Date Received | Submission |
|-----------------|---------------------------|
| May 28, 2021 | Roll 1 Submission |
| August 16, 2021 | Roll 2 Submission |
| August 24, 2021 | Roll 3 Submission (final) |

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8. ACRONYM KEY

List of abbreviations and acronyms

| Abbreviations/Acronyms | Description |
|------------------------|--|
| [REDACTED] | [REDACTED] |
| AHU | Air Handling Units |
| AQL | Acceptance Quality Limit |
| ASTM | Formerly Known as American Society for Testing and Materials |
| BI | Biological Indicator |
| BLA | Biologics License Application |
| BAS | Building Automation System |
| BMS | Building Management System |
| [REDACTED] | [REDACTED] |
| CBER | Center for Biologics Evaluation and Research |
| CCIT | Container Closure Integrity Testing |
| CFU | Colony Forming Units |
| CGMP | Current Good Manufacturing Practice |
| CHT | Clean Hold Time |
| CIP | Clean-In-Place |
| CNC | Controlled Non-Classified |
| COP | Clean-Out-of-Place |
| COVID-19 | Coronavirus Disease 2019 |
| CPP | Critical Process Parameter |
| [REDACTED] | [REDACTED] |
| DHT | Dirty Hold Time |
| (b) (6) | (b) (6) |
| DNA | Deoxyribonucleic Acid |
| DP | Drug Product |
| DS | Drug Substance |
| DSPC | 1,2-Distearoyl- <i>Sn</i> -Glycero-3-Phosphocholine |
| (b) (4) | [REDACTED] |
| EIR | Establishment Inspection Report |
| EM | Environmental Monitoring |
| EMS | Environmental Monitoring System |
| EU | Endotoxin Unit |
| EUA | Emergency Use Authorization |
| [REDACTED] | [REDACTED] |
| FDA | Food and Drug Administration |
| (b) (4) | [REDACTED] |

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| Abbreviations/Acronyms | Description |
|-------------------------------|--|
| HEPA | High Efficiency Particulate Air |
| HVAC | Heating, Ventilation, and Air Conditioning |
| (b) (4) | (b) (4) |
| IOQ | Installation and Operational Qualification |
| IQ | Installation Qualification |
| IR | Information Request |
| IRTD | Intelligent Resistance Temperature Device |
| ISO | International Organization for Standardization |
| (b) (4) | (b) (4) |
| (b) (4) | (b) (4) |
| (b) (4) | (b) (4) |
| (b) (4) | (b) (4) |
| LIMS | Laboratory Information Management System |
| LNP | Lipid Nanoparticles |
| MAL | Material Air Lock |
| MALL | Maximum Allowable Leakage Limits |
| MCB | Master Cell Bank |
| MCS | Manufacturing Control System |
| MOC | Material of Construction |
| MTC | Manufacturing Technology Center |
| MTCh | Material Transfer Chamber |
| MWCO | Molecular Weight Cut-Off |
| N/A | Not Applicable |
| NaCl | Sodium Chloride |
| NAI | No Action Indicated |
| (b) (4) | (b) (4) |
| NMT | No More Than |
| (b) (4) | (b) (4) |
| OAI | Official Action Indicated |
| OOS | Out-Of-Specification |
| OQ | Operational Qualification |
| OVR | Office of Vaccines Research and Review |
| PAL | Personnel Air Lock |
| PBS | Phosphate Buffered Saline |
| (b) (4) | (b) (4) |
| PE | Polyethylene |
| (b) (4) | (b) (4) |
| FTU | Freeze/Thaw Unit |

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| Abbreviations/Acronyms | Description |
|-------------------------------|---|
| Ph. Eur. | European Pharmacopoeia |
| PLC | Programmable Logic Controller |
| PLI | Pre-License Inspection |
| [REDACTED] | [REDACTED] |
| PPQ | Process Performance Qualification |
| PQ | Performance Qualification |
| PV | Process Validation |
| PW | Purified Water |
| RNA | Ribonucleic Acid |
| [REDACTED] | [REDACTED] |
| RoSS | Robust Storage and Shipping |
| (b) (4) | [REDACTED] |
| RPM | Revolutions Per Minute |
| RTS | Ready to Sterilize |
| RTU | Read to Use |
| SAP | Systems, Applications, and Products Enterprise Resource Planning Software |
| SAVI | Semi-Automatic Visual Inspection |
| SD | Static Division |
| [REDACTED] | [REDACTED] |
| SOP | Standard Operating Procedure |
| SS | Stainless Steel |
| STN | Submission Tracking Number |
| SUM | Single Use Mixer |
| SuS | Single use Support |
| TAMC | Total Aerobic Microbial Count |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| TCU | Temperature Control Unit |
| TCV | Temperature-Controlled Vehicle |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| TNTC | Too Numerous To Count |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |

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| Abbreviations/Acronyms | Description |
|------------------------|----------------------------|
| (b) (4) | |
| ULPA | Ultra-Low Particulate Air |
| USP | United States Pharmacopeia |
| v/v | Volume Per Volume |
| VAI | Voluntary Action Indicated |
| | |
| WCB | Working Cell Bank |
| WFI | Water for Injection |

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

ModernaTX, Inc. (Moderna) submitted documentation to BLA STN 125752/0 to support licensure of SPIKEVAX, a COVID-19 vaccine intended for the prevention of COVID-19 in adults ≥ 18 years of age. CBER/(b) (6) reviewed and evaluated the , DS, and DP manufacturing processes and facilities proposed for use in the manufacture of SPIKEVAX. Information reviewed, evaluated, and documented in this memo includes data to validate and support the consistency of the manufacturing process and product quality; facility information which includes utilities, cross-contamination prevention measures, and maintenance of controlled environments; and equipment for use in the manufacturing including qualification, cleaning and sterilization, and types of equipment used (i.e., dedicated, or shared, multi-use or single-use). Note, the facilities proposed for use in the manufacture of SPIKEVAX under the BLA are facilities that are currently in use for the manufacture of Moderna-COVID-19 Vaccine under EUA, which was originally issued on December 18, 2020.

As part of the BLA review, three PLIs were performed. The PLIs were performed at the (b) (4) (b) (4) (b) (4) manufacturing facility at Aldevron, LLC in Fargo, North Dakota (Aldevron) from November 1 – 5, 2021, the DS manufacturing facility at Moderna in Norwood, Massachusetts (Moderna) from October 25 – 29, 2021, and the DS manufacturing facility at Lonza Biologics, Inc. in Portsmouth, New Hampshire (Lonza) from October 18 – 22, 2021. Note, each PLI was documented in separate establishment inspection reports (EIR). At the conclusion of the Lonza PLI, a Form FDA 483 was issued on October 22, 2021 with four inspectional observations, which the firm responded to on November 12, 2021. A review of Lonza's responses is documented in a separate 483 response review memo. All inspectional 483 observations were deemed resolved, and the Lonza PLI was classified as Voluntary Action Indicated (VAI). No Form FDA 483 was issued at the conclusions of the Aldevron and Moderna PLIs. Both PLIs were classified as No Action Indicated (NAI).

In addition to the PLIs, facility inspections were waived for the DP manufacturing sites including: Catalent Indiana, LLC (subsidiary of Catalent Pharma Solutions, LLC), Bloomington, Indiana (Catalent) and Baxter Pharmaceutical Solutions, LLC, Bloomington, Indiana (Baxter). The inspection waivers were based on the evaluations of

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the facilities' inspection compliance histories. The inspection waivers are documented in a separate inspection waiver memo dated December 28, 2021.

Based on the review of the information submitted to BLA 125752/0 and in conjunction with the PLIs and inspectional compliance history evaluations, the production process, facilities, equipment, and controls appear acceptable for the licensure of SPIKEVAX, and approval is recommended.

B. RECOMMENDATION

I. APPROVAL

II. SIGNATURE BLOCK

| Reviewer/Title/Affiliation | Concurrence | Signature and Date |
|----------------------------|-------------|--------------------|
| (b) (6) | Concur | |
| (b) (6) | Concur | |
| (b) (6) | Concur | |
| (b) (6) | Concur | |
| (b) (6) | Concur | |

Module 3

3.2.S DRUG SUBSTANCE

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Table S.2.1-1 in the submission lists the drug substance (DS) manufacturing and testing facilities for SPIKEVAX.

| Site | FEI/DUNS Number | Responsibility |
|---|------------------------------------|---|
| Aldevron, LLC 4055 41st Avenue South Fargo, ND 58104 USA | FEI: 3015047170 DUNS: 048764943 | <ul style="list-style-type: none"> • Manufacture of (b) (4) (b) (4) (b) (4) . Release testing of (b) (4) (b) (4) |
| ModernaTX, Inc. One Moderna Way Norwood, MA 02062 USA | FEI: 3014937058 DUNS: 116912313 | <ul style="list-style-type: none"> • Manufacture, testing and storage of master cell bank and working cell bank. • Manufacture of CX-024414 <ul style="list-style-type: none"> - Including in-process, release, and stability testing (excluding (b) (4) for material manufactured at Lonza), storage. • Manufacture of (b) (4) <ul style="list-style-type: none"> - Including in-process, release, and stability testing (excluding (b) (4)), storage. • Manufacture of mRNA-1273 LNP <ul style="list-style-type: none"> - Including in-process, release, and stability testing (excluding (b) (4) testing for mRNA-1273 LNP manufactured at Lonza), storage. |

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| Site | FEI/DUNS Number | Responsibility |
|--|--|---|
| <p>ModernaTX, Inc. (b) (4) USA</p> | <p>FEI: (b) (4) DUNS: (b) (4)</p> | <ul style="list-style-type: none"> • CX-024414 quality control testing. <ul style="list-style-type: none"> - Release, stability, in-process testing (excluding (b) (4) for material manufactured at Lonza). • mRNA-1273 LNP quality control testing. <ul style="list-style-type: none"> - In-process, release, and stability testing (excluding (b) (4) testing for mRNA-1273 LNP manufactured at Lonza). |
| <p>Lonza Biologics, Inc. 101 International Drive, Portsmouth, NH 03801</p> | <p>FEI: 3001451441 DUNS: 093149750</p> | <ul style="list-style-type: none"> • Manufacture of (b) (4). <ul style="list-style-type: none"> - Including release and stability testing (b) (4) for material manufactured on-site), storage. • Manufacture of (b) (4). <ul style="list-style-type: none"> - Including release testing (b) (4) for material manufactured on-site), storage. • Manufacture of (b) (4). <ul style="list-style-type: none"> - Including release testing ((b) (4) manufactured on-site), storage. |
| <p>(b) (4)</p> | <p>(b) (4)</p> | <p>(b) (4)</p> |
| <p>(b) (4)</p> | <p>(b) (4)</p> | <p>(b) (4)</p> |

3.2.S.2.2 Description of Manufacturing Process

Description of CX-024414 mRNA Manufacturing Process

(b) (4)

3 pages have been determined to be not releasable: (b)(4)






Reviewer's comment: *The qualified shipping temperature and duration appears acceptable since it covers the bulk DS storage temperature and the recommended shipping duration.*

3.2.S.2.3 Control of Materials

Control of Materials – Source, History, and Generation of (b) (4) (Aldevron, Fargo)


Description of the (b) (4) Manufacturing Process

(b) (4)



3.2.S.2.5 Process Validation and/or Evaluation

(b) (4)



9 pages have been determined to be not releasable: (b)(4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The SPIKEVAX DP is a mRNA-lipid complex dispersion containing a mRNA (CX-024414) that encodes for the pre-fusion stabilized spike glycoprotein of 2019-novel Coronavirus (SARS-CoV-2) and four lipids that act as protectants and carriers of the mRNA. The four lipids are: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; DSPC (1,2-distearoylsn- glycer-3-phosphocholine); and cholesterol.

. The DP is supplied as a sterile, preservative-free, multiple-dose liquid, ready-to-use solution at 0.20 mg/mL for intramuscular administration in 10-mL (10R) vials closed with rubber stoppers and aluminum crimp flip-off seals in two vial presentations:

- **Maximum 11-dose (0.5 mL per dose) vial:** Each vial contains (b) (4) mg of CX-024414 mRNA and (b) (4) mg of SM-102 LNP as a white to off-white dispersion in a preservative-free buffer containing 20 mM Tris, (b) (4) acetate, 87 g/L sucrose at pH 7.5. The target fill volume is (b) (4) mL, which allows removal of a maximum of 11 doses per vial. The label fill volume is 5.5 mL.
- **Maximum 15-dose (0.5 mL per dose) vial:** Each vial contains (b) (4) mg of CX-024414 mRNA and (b) (4) mg of SM-102 LNP as a white to off-white dispersion in a preservative-free buffer containing 20 mM Tromethamine (Tris), (b) (4) acetate, 87 g/L sucrose at pH 7.5. The target fill volume is (b) (4) mL, which allows removal of a maximum of 15 doses per vial. The label fill volume is 7.5 mL.

3.2.P.2 Pharmaceutical Development

3.2.P.2.2. Drug Product

Reviewer's comment: *The firm provided studies to assess vial breakage in this section of the submission. The review of these studies is performed in Section 3.2.P.7, Container Closure System of this review memo.*

3.2.P.2.4 Container Closure System

The container closure systems used for manufacture of the commercial SPIKEVAX DP Include:

Vials

- (b) (4) 10R clear Type 1 borosilicate glass vial, meets (b) (4) requirements,
- (b) (4) 10-mL (b) (4) vial, meets (b) (4) requirements,
- (b) (4) 10R clear Type 1 equivalent alkali aluminosilicate glass vial, meets (b) (4) ,
- (b) (4) 10R clear Type 1 borosilicate glass vial, meets (b) (4) requirements.

Stoppers

- 20 mm (b) (4) stoppers, (b) (4) meets (b) (4) requirements,
- 20 mm (b) (4) stopper (b) (4), meets (b) (4) requirements.

Seal

- (b) (4) 20 mm (b) (4) aluminum seal with flip-off plastic cap

Reviewer's comment: Reference **Section 3.2.P.7** Container Closure System for description of container closure and stopper functional testing; and reference **Section 3.2.P.5.3** for container closure integrity testing (CCIT) evaluation.

The evaluation of suitability, chemical compatibility & resistance, extractables/leachables, safety of the materials of construction, biological activity, and photostability is deferred to OVR.

3.2.P.2.5 Microbiological Attributes

The manufacturing process utilizes pre-sterilized raw materials and supplies, High Efficiency Particulate Air (HEPA) -filtered classified production areas, and personnel gowning controls. During manufacturing, the formulated bulk DP is (b) (4) sterile filtered prior to being aseptically filled into vials. The sterilizing filter is (b) (4) integrity tested.

The final product storage conditions at -50 °C to -15 °C do not support microbial growth. The container closure system and its components were selected based on their ability to protect the quality of the product over its shelf life and have been qualified for use and storage.

The SPIKEVAX container closure system has been tested by the (b) (4) CCIT method and the testing provided acceptable data verifying that the stopper/vial/cap combination maintains integrity.

Reviewer's comment: Refer to **Section 3.2.P.5.3** for review of CCIT. In addition, an assessment of transportation stress was performed after which CCIT was executed on the study vials.

Microbial Challenge Hold Time Study

SPIKEVAX DP is preservative free due to the lipid nanoparticles incompatibility with common preservatives. The product is presented as a multiple-dose vial. A microbial challenge hold study was performed to evaluate the microbial resistance of the unpreserved multiple-dose DP.

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The microbial challenge hold time study was conducted per (b) (4) [(using the microorganism specified in (b) (4) and an additional (b) (4) in support of Moderna's proposed "In-Use Time" of 12 hours from initial needle puncture/vial entry for the DP.

The study (b) (4)

(note, the concentration of the commercial DP is 0.20 mg/mL).

(b) (4)

. This result supported the proposed 12 hours limit during which the SPIKEVAX DP solution inhibits the growth of common potential contaminant microorganisms at room temperature, and the 12 hours is set as the "In-Use Time" limit for DP. Firm also used the term "Beyond Use Time" to describe the same 12 hours limit from initial needle puncture/vial entry for the DP.

Reviewer's comment. *The microbial challenge hold time study results demonstrated that growth of microorganisms does not occur for up to (b) (4) hours in DP. The study appears acceptable to support Moderna's proposed "In-Use Time" of 12 hours.*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturers

Manufacturing and testing facilities for SPIKEVAX DP are listed in **Section 3.2.P.3.1**, *manufacturer(s)* of the submission, and is recreated in the table below.

| Site | FEI/DUNS Number | Responsibility |
|--|--|--|
| Catalent Indiana, LLC 1300 S Patterson Drive Bloomington, IN 47403 | FEI: 3005949964 DUNS: 172209277 | Fill/finish, packaging, labeling, in-process testing, release testing (sterility), storage |
| Baxter Pharmaceutical Solutions, LLC 927 S. Curry Pike Bloomington, IN 47403 | FEI: 1000115571 DUNS: 604719430 | Fill/finish, packaging, labeling, in-process testing, release testing (sterility), storage |
| (b) (4) | | |
| ModernaTX, Inc. One Moderna Way Norwood, MA 02062 | FEI: 3014937058 DUNS: 116912313 | Release and stability testing (excluding bacterial endotoxin and sterility testing), lot release |

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| Site | FEI/DUNS Number | Responsibility |
|---------|-----------------|----------------|
| (b) (4) | | |

3.2.P.3.3 Description of Manufacturing Process

The following sections describe the DP manufacturing process at the SPIKEVAX DP CMOs' facilities (i.e., Catalent and Baxter).

Table: DP Target Batch Size

| Site | Nominal Batch Size | Theoretical Number of Vials |
|----------|----------------------------|--|
| Baxter | (b) (4) mRNA (b) (4) DP | (b) (4) vials (b) (4) mL presentation) |
| Catalent | (b) (4) mRNA (b) (4) DP | (b) (4) vials (b) (4) mL presentation) (b) (4) vials (b) (4) mL presentation) |

Moderna generates batch numbers for commercial products in the material inventory system using the part number and the following logic (b) (4), where (b) (4) represents the (b) (4) represents the (b) (4) and (b) (4) represents a (b) (4). Moderna lot numbers are assigned to each DP batch to differentiate between unlabeled DP (UDP) which uses a (b) (4) series and labeled DP (LDP) which uses a (b) (4) series.


The manufacturing process for SPIKEVAX DP at Catalent follows the unit operation sequence: (b) (4)

Baxter employs a similar manufacturing sequence except that the (b) (4)


(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

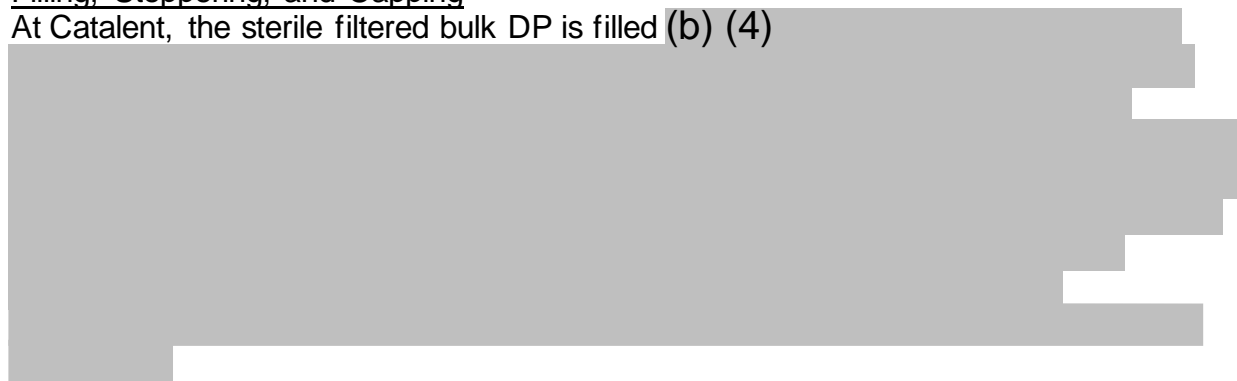
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(b) (4)

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Filling, Stoppering, and Capping

At Catalent, the sterile filtered bulk DP is filled (b) (4)

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(b) (4)

Visual Inspection

At the Catalent facility, all vials undergo 100% visual inspection either through a manual, semi-automated, or fully automated process. The automated visual inspection process can be combined with the manual or semi-automated visual inspection process. The Baxter facility implements (b) (4)

An acceptance quality limit (AQL) visual inspection is also performed. Vials that fail visual inspection are segregated from the batch as clearly labeled visual inspection rejects. (b) (4)

Labeling and Packaging

Vial labels are printed, or laser coded in-line with lot number and expiry dates and are applied to the inspected vials. Inspected and labeled vials are packaged 10 per carton along with a package insert. The carton is sealed and printed, or laser coded in-line with: Global Trade Identification Number (GTIN), lot number, expiry date, serial number. Twelve cartons are then placed into a shipping case and are stored.

(b) (4) Freeze and Storage

The (b) (4) step is used to ensure (b) (4) the DP vials (b) (4) final frozen storage. The packaged DP vials (b) (4)

(b) (4) the DP vials are stored in -20 °C (-25 °C to -15 °C) freezer.

| Manufacturing Site | Product Presentation | Freezer | Load Configuration | Duration ^(a) , (hours) |
|--------------------|----------------------|----------------|--------------------|-----------------------------------|
| Catalent | (b) (4) mL | (b) (4) -40 °C | (b) (4) | (b) (4) |
| | (b) (4) mL | (b) (4) -40 °C | (b) (4) | (b) (4) |
| Baxter | (b) (4) mL | (b) (4) -40 °C | (b) (4) | (b) (4) |

^a Durations are dependent on the freezer type, its refrigeration capacity, air flow patterns, and the load configuration.

Processing Durations

The cumulative DP processing duration includes the sum of the time under refrigeration at 2 to 8°C and the sum of time-out-of-refrigeration (TOR) at 20 to 25 °C. These parameters are provided in the table below. The cumulative process durations begin at

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the completion of thaw and end at the beginning of the (b) (4) freeze step. The cumulative process duration was qualified during hold-time qualification which was conducted as part of PPQ (refer to the hold-time qualification section of this review memo).

Table: Processing Duration Parameters

| Process Variable | Parameter Name | Range (Hour) | Site Qualified Range – Catalent (Hour) | Site Qualified Range – Baxter (Hour) |
|-----------------------------|---|--------------|--|--------------------------------------|
| Cumulative Process Duration | Cumulative process duration (2 to 8 °C, TOR, 20 to 25 °C) | (b) (4) | | |
| | *Cumulative TOR, (20 to 25 °C) | (b) (4) | | |

*The initial TOR provided under this BLA was revised to (b) (4) following an OVRR information request..

Reprocessing

Reprocessing is not performed for any DP process step. However, a (b) (4) validation protocol was submitted for the Catalent facility. Protocol VPPQ-256-100-00011-P, mRNA-1273 (Project Code 256-100/102) (b) (4) Protocol, will be used for failure in (b) (4) due to out of specification in-process controls in (b) (4). The (b) (4) will be considered validated once (b) (4) has been successfully performed on at least (b) (4) batches, meeting required acceptance criteria. The proposed change will be reported as a future CBE-30 supplement.

Reviewer's comment regarding reprocessing: The Catalent reprocessing protocol was reviewed for parameters under (b) (6) purview, which appear acceptable. The review of all other parameters is deferred to OVRR.

Reviewer's comment regarding the DP manufacturing process: Each step of the SPIKEVAX DP manufacturing process was described, including the slight differences in manufacturing at Catalent and Baxter. The information provided appears acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates (Catalent and Baxter)

The CPPs and their PARs (Proven Acceptable Ranges) for the DP manufacturing process were provided in **Section 3.2.P.3.4.1** of the submission and are summarized in the table below.

Table: Critical Process Parameters

| Process Step | Critical Process Parameter | PAR | CQA Impact | Rationale |
|--------------|----------------------------|-----|------------|-----------|
| (b) (4) | | | | |

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| Process Step | Critical Process Parameter | PAR | CQA Impact | Rationale |
|-----------------------------|---|--|-------------|--|
| Stoppering, and Capping | (b) (4) | <u>Catalent:</u> (b) (4) <u>Baxter:</u> (b) (4) | Sterility | If improperly sealed, the DP is at risk of sterility breach and patient safety |
| Cumulative Process Duration | Cumulative Process Duration (2 to 8°C, and TOR 20 to 25 °C) | (b) (4) | mRNA Purity | Scored CPP as longer than specified processing times are unlikely to cause a failed batch, but may significantly impact mRNA-1273 CQAs |
| Cumulative Process Duration | Cumulative Process Duration (TOR, 20 to 25 °C) | (b) (4) | mRNA Purity | Scored CPP as longer than specified processing times are unlikely to cause a failed batch, but may significantly impact mRNA-1273 CQAs |

^a OOS: Out-of-Specification

Details of the characterization studies conducted for the CPPs were submitted in the BLA's **Section 3.2.P.2.3.1.2**. Characterization of stoppering, and capping operations was based on CCIT. The cumulative process duration was determined using data from developmental hold-time studies and manufacturing experience with batches manufactured at Moderna and Catalent, where mRNA purity losses of DP samples exposed to (b) (4) TOR (20 to 25 °C) and cumulative process duration of (b) (4) (at 2 to 8 °C and TOR) were evaluated.

Reviewer's comment: See **Section 3.2.P.7** of this review memo for CCIT information. All other characterization studies (including studies for dilution and cumulative process duration) are deferred to OVR.

Microbial Control Strategy (Catalent and Baxter)

The SPIKEVAX DP manufacturing process is performed in a Grade (b) (4) manufacturing area, with final fill finish conducted on filling lines in a Grade (b) (4) environment. At Catalent, the filling lines include a Grade (b) (4) while Baxter utilizes a filling machine within a Grade (b) (4) (b) (4) surrounded by a Grade (b) (4) background. Dilution buffer is (b) (4) and then (b) (4).

All assemblies, storage bags, and product contact filling components used in the manufacturing of DP at the Catalent facility are single use. Manufacturing operations in the Baxter facility utilize dedicated multi-use or single-use sterile materials for product contact equipment. Aseptic connections are used for closed processing at both facilities. Sterility of the automated filling line is demonstrated through media fill qualification as described in **Section 3.2.P.3.5**. EM of the manufacturing areas is performed. Sterilization and CCIT of the container closure system is conducted. Any deviations incurred in the implementation of microbial controls are assessed for product quality impact.

Reviewer's comment: *The microbial controls in-place at both Catalent and Baxter are reviewed for acceptability in their specific sections below.*

Critical In-Process Control Testing (Catalent and Baxter):

The critical in-process control (CIPC) testing for the DP manufacturing process are summarized in the table below.

Table: Critical In-Process Controls

(b) (4)

Other critical in-process control testing performed include: (b) (4)

Reviewer's comment: *The controls appear to provide an appropriate strategy for monitoring product quality and process consistency of the DP manufacturing process.*

3.2.P.3.5 Process Validation and Evaluation

Process validation was performed to qualify DP manufacturing for each manufacturing site, fill volume, filling line and container closure. The PPQ data are reviewed in the following sections.

Process Performance Qualification (Catalent)

- (b) (4)

10 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.7 Container Closure System

Bulk DP is filled into 10 mL vials and closed with a 20 mm stopper and 20 mm aluminum seal within an (b) (4), after which the vials are packaged in a secondary carton. The container closure types qualified for use in each fill/finish facility are as follows:

Vials:

- (b) (4) **10R RTU** (b) (4) : Both the (b) (4) RTU and (b) (4) vials are supplied by (b) (4). (b) (4) RTU vials are received sterile (b) (4). The vials are sterilized (b) (4) by the supplier and are used for DP filling (both (b) (4) mL and (b) (4) mL fill volumes) on the (b) (4) at Catalent.

The (b) (4) 10R (b) (4) vials are (b) (4). It is used for DP filling (both (b) (4) mL and (b) (4) mL fill volumes) on (b) (4) at Catalent.

(b) (4)

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

- (b) (4)

(b) (4)

Stoppers: All stoppers (b) (4) RTU, (b) (4) RTU and (b) (4) used in the manufacture of SPIKEVAX DP are supplied by (b) (4).

- (b) (4) RTU and (b) (4) RTU: The RTU 20 mm (b) (4) stoppers are received (b) (4) from the supplier. The (b) (4) RTU stoppers are used for stoppering all filled vial types at Catalent (i.e., (b) (4) for both (b) (4) mL and (b) (4) mL fill volumes.

Table: (b) (4) RTU and (b) (4) RTU Stopper dimensions

(b) (4)

- (b) (4)

(b) (4)

Reviewer's comment: *The stoppers appear to be dimensionally equivalent.*

Seals

The 20 mm flip-off red matte aluminum seals are received RTU (b) (4). The seals are (b) (4) by the supplier (b) (4). The seals are used for all stoppered vials at both Catalent and Baxter.

Secondary Packaging

The secondary packaging for DP is an assembled, labeled multi-vial carton affixed with a tamper-evident seal or glue closed containing labeled vials; a total of ten DP vials per carton in a 2-by-5 configuration. Each carton is then placed into a case containing a total of twelve cartons: total of 120 vials per case. The case is then closed with a tamper-evident seal.

Studies Performed to Validate Container Closure

- **Vial Breakage Studies**




(b) (4)

The study is described as follows:

- (b) (4) **mL fill study:** (b) (4)

- (b) (4) **mL fill study:** (b) (4)


(b) (4)



Reviewer's comment: The studies conducted on the (b) (4) vials were performed at the DP long term storage temperature and no vial breakages were observed. Based on the information provided, the assessment appears acceptable, and the justifications provided for the 10 mL (b) (4) vials appear reasonable.


- **Stopper Functionality Testing**

Stopper functionality tests performed include (b) (4)



. The results are presented in the tables below.

(b) (4)



(b) (4)

(b) (4)

- **Container Closure Integrity Testing:** (b) (4) conducted the CCIT using the (b) (4) method. (b) (4) strategy was used to demonstrate microbiological suitability of the primary container closure systems using CCIT, for each fill line. (b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

(b) (4)

[REDACTED]

[REDACTED]




[REDACTED]

(b) (4)


[REDACTED]

[REDACTED]

(b) (4)



(b) (4)



MODERNATX, INC., NORWOOD, MA: DRUG SUBSTANCE MANUFACTURING AND DS/DP RELEASE AND STABILITY TESTING

ModernaTX, Inc.'s Manufacturing Technology Center (MTC) is a multi-product manufacturing and testing site for mRNA-based products. No FDA-approved product is currently manufactured at the facility. Moderna's Norwood site currently manufactures clinical products such as plasmid DNA, formulated lipid nanoparticles, mRNA-based DP, and personalized cancer vaccines.

There are (b) (4) buildings of interest at the Moderna Norwood site:

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(b) (4)

(b) (4)

Manufacturing Areas

Moderna Norwood is designed to accommodate multiple manufacturing operations. All rooms used for the manufacture of SPIKEVAX at Moderna are classified Grade (b) (4). The manufacturing areas are as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: The facility appears suitably sized and adequately designed to manufacture SPIKEVAX DS. CBER and (b) (6) conducted a PLI for the Moderna Norwood manufacturing site from October 25 to 29, 2021, and the inspection was classified NAI.

Manufacturing Flow

The flow of materials, equipment, waste, and personnel are guided by established and approved procedures for the purposes of controlling contamination and preventing cross-contamination. The manufacturing flows at the Moderna facility include:

- **Personnel Flow and Gowning:** Procedures and programs are established at Moderna for personnel hygiene practices, gowning procedures, and controlled personnel flow in the manufacturing areas. Per these procedures, no personnel who are ill, have infections, or have open wounds are permitted to enter cleanrooms under any circumstances. All cleanroom suites have separate airlocks for gowning and de-gowning activities. Exit from one cleanroom production suite must occur through gown-out areas and fresh gowning attire must be donned prior to entering other cleanroom suites.

Facility access is controlled by (b) (4) which restrict entry to authorized personnel only. Additional measures of control are maintained through procedures and defined restrictions as required by activity and area classification. Traffic flow within CNC (controlled not classified) areas may be

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either unidirectional or bi-directional; however, movement in Grade (b) (4) and cleaner areas is strictly (b) (4). All personnel are required to remove make-up, jewelry, and accessories, and to wash or sanitize hands before gowning. Shoe covers are placed over company dedicated shoes, which are either kept in adjacent locker rooms or disinfected with (b) (4) while crossing the line of demarcation at gowning room entry ways. A gowning qualification assessment is required prior to working in Grade (b) (4) manufacturing areas.

- **Waste Flow:** Waste containment and transportation are defined in controlled procedures for the manufacturing areas at the Norwood campus. Prior to being transported, waste is labeled accordingly. Biohazardous substances are contained in red biohazard bags, sharps containers are properly closed, and regulated liquids are contained in a secondary container. All chemicals are disposed of according to OSHA, EPA, state, and local regulations.

For all manufacturing processes, following transport to proximal CNC corridors, wastes are transported through a series of additional CNC and uncontrolled corridors to uncontrolled waste storage room# (b) (4) for removal from the building.

- **Materials and Equipment Flow:** Procedures control the transport, sanitization, disinfection, and personnel responsible for material and equipment transfer into and out of cleanroom manufacturing areas at the Moderna facility. Before entering a controlled area, all equipment, materials, and supplies are sanitized at designated airlocks. All buffer prep, mRNA, and LNP (b) (4) process transfers are completed between the CNC alcove area and dedicated Grade (b) (4) transfer airlocks for each clean suite.

Reviewer's comment: The submitted facility flow diagrams were reviewed and found acceptable. All manufacturing areas are access controlled. (b) (4) flow of personnel appears to be implemented in Grade (b) (4) (and above) areas. Note, Moderna's SPIKEVAX DS is (b) (4) -controlled so no aseptic processing is conducted.

Facility Cleaning

Facility cleaning at Moderna is performed per established procedures. (b) (4)



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Reviewer's comment: *The cleaning frequency and cleaning agents appear suitable for the mitigation of contamination and cross contamination in the manufacturing areas. The facility cleaning appears acceptable. The disinfectant efficacy study was not provided in the BLA but was covered during the PLI and was deemed acceptable.*

Room Changeover

Room changeover is executed per established procedures. The changeover process (b) (4)

Reviewer's comment: *The manufacturing suites are dedicated to SPIKEVAX DS manufacturing. The room changeover activities appear acceptable.*

Process Operations: All SPIKEVAX DS manufacturing processes are performed under (b) (4) processing, except for the (b) (4) step which are performed under (b) (4) processing within a (b) (4)

Environmental Monitoring

EM for the manufacturing areas is performed per procedure. Routine EM consists of (b) (4) monitoring. The Grade (b) (4) areas are sampled (b) (4). CNC areas are sampled (b) (4)

(b) (4)

(b) (4)

For the DS processes, there are no critical operations that require Grade (b) (4) in the MTC-^{(b) (4)} facility. (b) (4)

(b) (4) to provide an additional layer of microbial control. However, these are not considered critical operations. EM and personnel monitoring is not required for (b) (4) supporting the DS processes (during the manufacturing process). Routine EM is performed for these (b) (4)

Quarterly trend reports for EM are generated at the end of each quarter. The level of escalation for alert level trends and action level excursions is commensurate with the severity of the event. Any single result that yields mold or exceeds the alert or action level is communicated to QC, quality assurance, and area management. All excursions are reviewed on a (b) (4) basis.

Reviewer's comment: Moderna's statement regarding non-performance of personnel monitoring during the (b) (4) steps (within the (b) (4) of DS manufacturing appears acceptable. The DS manufacturing process is (b) (4) controlled, and the (b) (4) Routine (b) (4) monitoring is performed (b) (4). The EM program appears acceptable.

UTILITIES


Critical utilities include HVAC, WFI, process water, process gases and computer systems.

Heating, Ventilation and Air Conditioning (HVAC) Systems


Cleanrooms and laboratories at Moderna's Norwood site are conditioned with semi-custom, roof mounted air handling units (AHUs) with HEPA filtration and (b) (4)

(b) (4)

(b) (4)




(b) (4)




Water for Injection (WFI)

(b) (4)



(b) (4)



Process Water: (b) (4)



Process Gases: (b) (4)

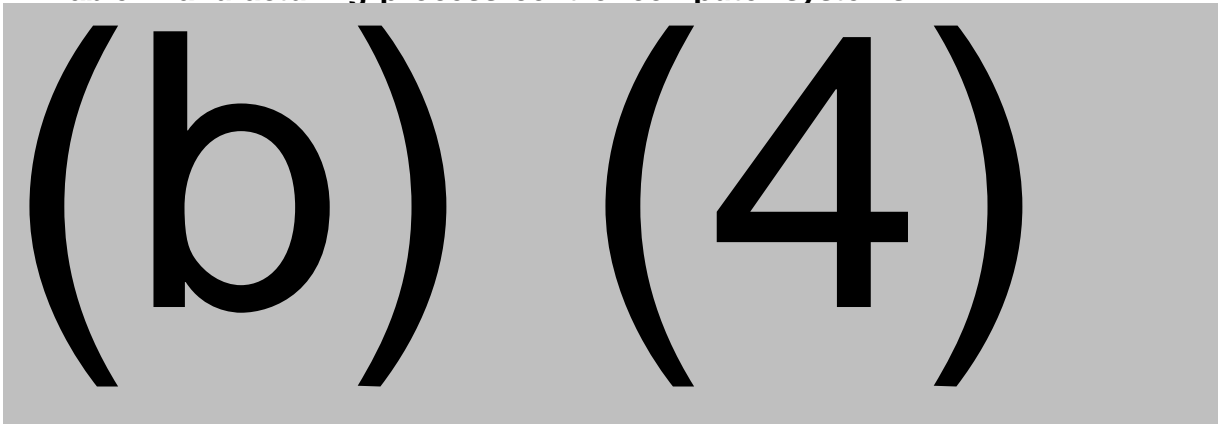


Reviewer's comment: Moderna appears to have established control over the critical utilities at their Norwood facility, with regular monitoring and trending.

Computer Systems:

All computerized systems used in manufacturing are installed, validated, maintained, and supported in accordance with appropriate regulations and guidance, including 21 CFR Part 11. Quality assurance is responsible for approving lifecycle plans and new and revised documentation including procedures and change controls created for newly acquired software and for approving all changes to existing systems. Systems are tracked as either supporting systems or manufacturing process control systems and related changes are periodically reviewed.

Table: Manufacturing process control computer systems



(b) (4)



Reviewer's comment: A general description of the computer systems controlling the manufacturing processes was provided and reviewed. The computer systems are validated and appear acceptable.

Prevention of Contamination/Cross-Contamination

The Moderna Norwood facility operates as a multi-product facility for mRNA-based products. Access to the manufacturing areas is controlled by a (b) (4) system and is limited to authorized personnel. The clean rooms are designed to provide a controlled environment for production of bulk biopharmaceuticals. Room pressurization, airlocks and gown rooms facilitate product/process separation and containment. The surface finishes in the manufacturing areas are consistent with the intended function of the area and were designed for durability and ease of cleaning. The manufacturing trains are dedicated to SPIKEVAX DS.

Contamination controls at the facility include (b) (4)

Environmental conditions are monitored and alarmed for excursions. A formal level-based training program is used to ensure manufacturing and laboratory personnel are appropriately trained and qualified. Other programs at the Moderna facility for prevention of contamination/cross-contamination include: a formal gowning process, EM program, and established personnel, material, product, and waste flow paths throughout the facility. SPIKEVAX manufacturing processes primarily implement single-use technology. In addition, validated cleaning and disinfection processes for reusable equipment and facilities are implemented.

Reviewer's comment: *The measures in-place appear acceptable.*

Equipment

Manufacturing processes for SPIKEVAX DS utilize a dedicated set of equipment. A combination of reusable non-product contact equipment, single-use disposable product-contact equipment, and reusable product-contact equipment are used in the manufacture of SPIKEVAX DS. Non-product contact manufacturing equipment includes (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

LONZA BIOLOGICS, PORTSMOUTH, NEW HAMPSHIRE: DS MANUFACTURING AND DS RELEASE TESTING

Lonza is a CMO for the SPIKEVAX DS. The Lonza Portsmouth site is a multi-product facility that manufactures clinical phase allogeneic and autologous cell-based products such as: (b) (4)

[REDACTED]

Procedures are in place governing the introduction of new products to the facility following a risk assessment.

The Lonza Portsmouth facility consists of (b) (4)

[REDACTED]

[REDACTED]

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SPIKEVAX DS manufacturing areas are (b) (4)




Manufacturing areas associated with the SPIKEVAX DS are product dedicated.

Reviewer's comment: *The facility appears to have adequate space to perform manufacturing of SPIKEVAX DS. Note, the same manufacturing process implemented at Moderna for SPIKEVAX DS manufacture is applied at Lonza. CBER and (b) (4) performed a PLI at Lonza from October 18 to 22, 2021 and it was classified VAI. The firm responded to the Form FDA 483 and the responses were acceptable.*

Manufacturing Flows

- Personnel flow, access, and gowning: To minimize the risk of product contamination, entry into manufacturing areas is granted through (b) (4) access, which is dependent on meeting gowning qualification requirements. Initial entry into the Lonza Portsmouth manufacturing areas is (b) (4)
- 
- 


(b) (4)



Reviewer's comment: Moderna provided the Lonza facility flow diagrams in the submission. The flow diagrams were reviewed and found acceptable.

Facility Cleaning

(b) (4)



Cleaning equipment (b) (4) is dedicated to a specific room classification and labelled. (b) (4)

Cleaning and sanitization of the manufacturing suites are documented. The effectiveness of the cleaning methods employed is monitored routinely through the EM program.

Approved cleaning and disinfectant agents used in the (b) (4)



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Room and equipment release are performed as required per written procedures.

Reviewer's comment: *The frequency of cleaning appears acceptable for the degree of manufacturing performed. The disinfectant agents and rotations also appear acceptable.*

- **Disinfectant Efficacy Qualification:** Disinfectant efficacy studies were performed to qualify the disinfectants in accordance with (b) (4)

Reviewer's comment: *The study was performed per acceptable standards and met all acceptance criteria. The information appears acceptable.*

Contamination and cross-contamination controls

In addition to the controls described above, the following contamination/cross-contamination measures are in place at the Lonza facility:

(b) (4)

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(b) (4)



Reviewer's comment: *The contamination/cross contamination mitigation measures present at Lonza appear acceptable.*


Environmental Monitoring

An EM program is in place for the (b) (4) cell therapy facility. The program includes (b) (4) monitoring of production areas and laminar flow environments, and appropriate (b) (4) monitoring, including personnel monitoring. Grade (b) (4) and Grade (b) (4) areas associated with mRNA manufacturing are monitored (b) (4) for (b) (4). The EM action limits implemented in the mRNA manufacturing rooms are in accordance with ISO cleanroom standards.

The (b) (4) EM action limits implemented in the mRNA manufacturing rooms are as follows:

(b) (4)

(b) (4)



Reviewer's comment: *EM Alert limits were not submitted in the BLA. Lonza representatives stated during the PLI that alert limits are currently being established for the mRNA manufacturing rooms. The firm stated that they are trending per historical data from other rooms in the Cell Therapy facility. This is acceptable since the mRNA suites are newly constructed.*

Utilities

HVAC

(b) (4)

(b) (4)

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All EMPQ results met all acceptance criteria.

Reviewer's comment: The EMPQ was conducted under (b) (4) conditions. EMPQ reports for AHUs were submitted and appear acceptable. The HVAC system's control and monitoring appear acceptable.

Water System

(b) (4)

1 page has been determined to be not releasable: (b)(4)

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Reviewer's comment: *The utilities are qualified and undergo routine sampling per the firm's procedures. The latest utility trend report was provided in the submission, was reviewed, and appears acceptable. Note, computer systems information was not provided in the BLA but was reviewed in detail during the PLI and was deemed acceptable.*

Equipment

All equipment items used in the manufacture of SPIKEVAX DS at Lonza are dedicated. The manufacture of SPIKEVAX DS is conducted on manufacturing train (b) (4) (which is the sole SPIKEVAX DS train at Lonza). The same equipment types (including their single use/disposable/contact designations) listed for use at Moderna are implemented at Lonza. All equipment used for manufacture of SPIKEVAX DS underwent qualification at Lonza, and all qualification activities met all acceptance criteria. The following equipment qualification information was also reviewed.

- (b) (4)

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(b) (4)

(b) (4)

(b) (4)

- (b) (4)

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment for Equipment: Lonza uses the same equipment types as Moderna, including their use designations e.g., single use, disposable, product/non product contact. Lonza only uses the (b) (4)

Representative summary reports for all equipment types were submitted and they appear acceptable. All equipment was qualified and met acceptance criteria.

Equipment Cleaning

The SPIKEVAX DS manufacturing processes use product dedicated and single use disposable equipment. The reusable product contact equipment includes

(b) (4)

All other product contact equipment is single use disposable.

(b) (4)

Reviewer's comment: The product contact equipment is subjected to cleaning verification since cleaning validation is ongoing at Lonza. This is acceptable. The single use and disposable nature of most equipment implemented for SPIKEVAX DS manufacture appears to reduce the risk of contamination/cross contamination from improper cleaning/sanitization.

CATALENT INDIANA, LLC (SUBSIDIARY OF CATALENT PHARMA SOLUTIONS, LLC), BLOOMINGTON, INDIANA: DRUG PRODUCT MANUFACTURING FACILITY

SPIKEVAX DP is filled at Catalent's Bloomington, Indiana facility. Catalent is a wholly owned CMO and indirect subsidiary of Catalent Pharma Solution, Inc. Catalent is a

multi-product manufacturing facility which includes (b) (4)

[Redacted]

- [Redacted]
- [Redacted]

The site includes (b) (4) buildings; (b) (4)

[Redacted]

[Redacted]

Manufacturing Areas

Classified rooms which may be used for SPIKEVAX DP manufacturing activities are provided in the table below.

Table: Manufacturing Rooms

(b) (4)

(b) (4)

Prevention of Contamination/Cross Contamination

Catalent is a multi-product manufacturing site. Products may share manufacturing areas and indirect or non-product contact multi-use equipment. Product contact parts are disposable, or client dedicated. Contamination/cross-contamination mitigation processes including temporal segregation, physical segregation, and validation/verification of cleaning procedures, area clearance and sample testing are in place to ensure that potential carryover between clients/products meets pre-defined safety limits.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)




(b) (4)



(b) (4)



(b) (4)



Reviewer's comment: *The facility cleaning schedules, and cleaning agents*
(b) (4) *appear*
acceptable for sanitization of the manufacturing area.



Utilities

HVAC

DP manufacturing areas at Catalent (b) (4)





(b) (4)



Environmental Monitoring


Catalent has an EM program. (b) (4)



(b) (4)

(b) (4)

(b) (4)



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(b) (4)

Reviewer's comment: Catalent is an approved manufacturing facility. No modifications were reported under the current BLA. The HVAC system was qualified and appears to undergo routine monitoring. Alert and Action limit appear suitable for the room classifications. EM is trended, and excursions are investigated per procedure. The EM appears acceptable.

WFI

(b) (4)

Clean Compressed Air

(b) (4)

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Utilities are trended and monitored, and out-of-level results are investigated for potential impact. Details of the investigation include historical data, circumstances surrounding the failure or trend, and root cause.

Reviewer's comment: *The critical utilities at Catalent are monitored and trended. The utilities have been reviewed during many past FDA inspections. The information appears acceptable.*

Equipment

The process operations of the SPIKEVAX DP manufacturing are summarized in the table below.

Table: SPIKEVAX Process Operations

| Process Step | Open or Closed Processing | Cross Contamination Mitigation |
|------------------------------|---------------------------|--------------------------------|
| (b) (4) | (b) (4) | (b) (4) |
| | | |
| | | |
| | | |
| Dilution | | (b) (4) |
| Sterile Filtration | | (b) (4) |
| Filling, Stoppering, Capping | | (b) (4) |

All product contact equipment used in the SPIKEVAX DP manufacturing process is single use and disposable. SPIKEVAX DP single use, disposable consumables including (b) (4)

Non-product contact equipment for the manufacture of SPIKEVAX DP is (b) (4)

DP using the (b) (4)

7 pages have been determined to be not releasable: (b)(4)

(b) (4)




Reviewer's comment: *All product contact equipment are single use and disposable. Cleaning verification is conducted for non-product contact equipment. The equipment cleaning process appears acceptable.*

BAXTER PHARMACEUTICAL SOLUTIONS, LLC (BAXTER), BLOOMINGTON, INDIANA:

DP MANUFACTURING FACILITY

Baxter's Bloomington facility is a CMO currently manufacturing FDA approved products using the same fill line/formulation areas and utilities as proposed for the manufacture of SPIKEVAX DP.

(b) (4)



SPIKEVAX DP is manufactured in a (b) (4)



(b) (4)

(b) (4)

Baxter Bloomington is a licensed facility with FDA inspection history. All inspections since 2015 were either VAI or NAI and includes the most recent FDA inspection conducted November 2-10, 2021 that covered rooms, equipment, and processes in support of the manufacture of SPIKEVAX (inspection classified as VAI). Other products manufactured at Baxter include:

(b) (4)

(b) (4)

(b) (4)


Reviewer's comment: *The manufacturing area appears to be of suitable size for the proposed unit operations. The Baxter facility is an existing facility with an acceptable FDA compliance history. The products manufactured at Baxter do not appear to pose a significant risk to the manufacture of SPIKEVAX. The information appears acceptable.*

Prevention of Contamination/Cross Contamination

Dedicated and single-use equipment is utilized for all biological products (including SPIKEVAX) manufactured at the Baxter facility. In addition, cross-contamination measures have been established to prevent the cross-contamination of materials, products, and equipment.




Adequate gowning is required for classified areas. (b) (4)

(b) (4)



Reviewer's comment: *Baxter's facility flow diagrams (material, personnel, product, and waste) were reviewed and appear acceptable.*

Cleaning: (b) (4)







Reviewer's comment: *The cleaning procedures appear acceptable.*

Utilities

HVAC



(b) (4)



Reviewer's comment: *The HVAC information submitted appears acceptable.*

Environmental Monitoring

(b) (4)



(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: Baxter's EM strategy appears acceptable. EM program site selection was based on the initial EMPQ results and sampling frequency appears acceptable.

WFI: (b) (4)

Reviewer's comment: Baxter WFI specifications are in accordance with (b) (4) standards, and the system appears acceptable.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED]

- **Inspection, Labeling and Packaging Equipment:** Finishing equipment supporting the automated inspection, labeling, and packaging of the SPIKEVAX finished product vials manufactured at Baxter is in Building (b) (4) and all have been qualified for the intended use. Finishing equipment is not dedicated and has no direct product contact.

- (b) (4) [REDACTED]

1 page has been determined to be not releasable: (b)(4)

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Reviewer's comment: *The equipment items listed in this section were qualified and met the respective acceptance criteria. The information appears acceptable.*

- **Stopper (b) (4)** : The 20 mm stoppers used for the manufacture of the SPIKEVAX DP are (b) (4) in Building (b) (4)

(b) (4)

(b) (4)

Reviewer Comments: *The stopper (b) (4) was qualified, and the acceptance criteria were met. The information appears acceptable.*

(b) (4)

(b) (4)


Equipment Sterilization

(b) (4)

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)



Reviewer Comments: *The cleaning validation conducted for SPIKEVAX DP reusable product contact equipment met acceptance criteria and appears acceptable.*