



**U.S. FOOD & DRUG**  
ADMINISTRATION

**To:** EUA 27073

**From:**

**Through:**

**CC:**

(b) (6)

(b) (6)

**Sponsor:** ModernaTX

**Product:** COVID-19 Vaccine (mRNA-1273)

**Indication:** Prevention of COVID-19 in adults ≥18 years of age

**Subject:** Review of EUA 27073 and corresponding ModernaTX IND 019745, (b) (4)

amendments regarding manufacturing facilities for Moderna's COVID -19 vaccine mRNA-1273.

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**Recommendation:** We have reviewed the information submitted to EUA 27073 and cross referenced in IND 19745, (b) (4) and (b) (4) for the manufacturing facilities for Moderna's COVID-19 vaccine, mRNA-1273 (hereafter mRNA-1273), DNA plasmid, drug substance, LNP/formulated bulk, and drug product, as well as additional drug product release testing facilities. We find the facilities, equipment, and controls appear acceptable for the manufacture of this product to be used under an Emergency Use Authorization (EUA).

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#### **Executive summary**

The manufacture of mRNA-1273 is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information as per the guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19, October

2020”, to ensure that there is adequate control of the manufacturing processes and facilities.

FDA performed a site visit, reviewed inspectional histories of the facilities and all available information to ascertain whether each facility meets current good manufacturing practice requirements. We find that all the facilities are adequate to support the use of the Moderna COVID-19 vaccine under an Emergency Use Authorization.

Please see the table below for the manufacturing facilities, their activities, and their compliance status.

**Table: Manufacturing Sites, Activities, and Compliance Status (Recent FDA Inspections)**

| FDA Establishment Identification number (FEI, DUNS) | Name of facility owner and indicate if owner is a CMO | Activity of facility (e.g., Drug Substances/ Intermediates/ Drug Product/Finished Device manufacturer Testing/Labeler/ Packager) | Location (US and Non-US) | Associated NDA, BLA, IND, or IDE | Corporate Sponsor or Applicant | Date of Most Recent Site Visit or Inspection |            |
|-----------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------------------|--------------------------------|----------------------------------------------|------------|
| FEI: 30167441856                                    | ModernaTX                                             | Plasmid DS manufacturing Release testing                                                                                         | Norwood, MA              | IND 19745                        | ModernaTX                      | Oct. 13 - 16, 2020 <sup>1</sup>              | Acceptable |
| FEI: 3001451441                                     | Lonza Biologics, Inc.                                 | DS manufacturing                                                                                                                 | Portsmouth, NH           |                                  |                                | Oct. 28 – Nov. 3, 2020                       | Acceptable |
| FEI: 300594964<br>DUNS: 172209277                   | Catalent Biologics, Catalent Indiana LLC              | DP manufacturing Release Testing                                                                                                 | Bloomington, IN          |                                  |                                | Aug 27 – Sep 02 2020 <sup>2</sup>            | Acceptable |
| FEI: 1219145<br>DUNS: 076574078                     | Associates of Cape Cod                                | Release Testing                                                                                                                  | East Falmouth, MA        |                                  |                                | Nov 19 – 26, 2019 <sup>2</sup>               | Acceptable |

DS: Drug Substance DP: Drug Product IVT: *in vitro* transcription LNP: Lipid Nanoparticle

<sup>1</sup>Site visit conducted by FDA

<sup>2</sup>Inspection conducted by FDA

## I. Manufacturing information and review

Information regarding the manufacturing processes and facilities used for mRNA-1273 was submitted to IND 019745, (b) (4)

(b) (4). The following amendments containing that information were thoroughly reviewed:

Table of IND 019745, (b) (4), and (b) (4) amendments reviewed for the EUA

| IND 19745 Amendments | (b) (4) |
|----------------------|---------|
| 13                   | (b) (4) |
| 30                   |         |
| 39                   |         |
| 41                   |         |
| 66                   |         |
| 67                   |         |
| 70                   |         |
| 81                   |         |
| 82                   |         |
| 84                   |         |
| 89                   |         |
| 92                   |         |

#### A. Container closure integrity testing (CCIT) studies

The container-closure system for the mRNA-1273 drug product consists of three different vial types with identical dimensions. They all use the same stopper and seal combination as noted in the table below:

| Fill Line                        | Presentation                      | Container Closure Component                  | Material of Construction(a)                           |
|----------------------------------|-----------------------------------|----------------------------------------------|-------------------------------------------------------|
| Flexible Filling Line<br>(b) (4) | mRNA-1273 Drug Product<br>(b) (4) | Vial, Ompi® 10R, sterile, for human use      | Type 1 borosilicate glass, clear                      |
|                                  |                                   | Stopper, (b) (4), 20 mm, Ready-to-Use        | (b) (4)                                               |
|                                  |                                   | Seal, (b) (4), 20 mm, Red Matte flip-off     | Aluminum seal with flip-off plastic cap; color Red    |
|                                  | mRNA-1273 Drug Product<br>(b) (4) | Vial, SIOPlas™ 10-mL, sterile, for human use | Cyclic Olefin Polymer (COP)                           |
|                                  |                                   | Stopper, (b) (4), 20 mm, Ready-to-Use        | (b) (4)                                               |
|                                  |                                   | Seal, (b) (4) 20 mm, Red Matte flip-off      | Aluminum seal with flip-off plastic cap; color Red    |
| Vial Line<br>(b) (4)             | mRNA-1273 Drug Product<br>(b) (4) | Vial, Corning Valor® 10R, (b) (4)            | Type 1 equivalent alkali aluminosilicate glass, clear |
|                                  |                                   | Stopper, (b) (4), 20 mm, Ready-to-Use        | (b) (4)                                               |
|                                  |                                   | Seal, (b) (4) 20 mm, Red Matte flip-off      | Aluminum seal with flip-off plastic cap; color Red    |
|                                  | mRNA-1273 Drug Product<br>(b) (4) | Vial, Ompi® 10R, (b) (4)                     | Type 1 borosilicate glass, clear                      |
|                                  |                                   | Stopper, (b) (4), 20 mm, Ready-to-Use        | (b) (4)                                               |
|                                  |                                   | Seal, (b) (4) 20 mm, Red Matte flip-off      | Aluminum seal with flip-off plastic cap; color Red    |

A non-product specific and product specific CCIT were completed by the container closure system (CCS) vendor (b) (4) using

the (b) (4) method. This CCIT was conducted as an engineering study (#ENG20037) to verify the suitability of the CCS to form an integral seal under long-term storage conditions [-20°C (-15°C to -25°C)]. The initial study for CCIT was performed on the Ompi® vials and involved comparing the observed (b) (4) of the 10R vial container closure system (b) (4)

The optimum (b) (4) (b) (4) was determined, and an operating range was established. The (b) (4) method used is a sensitive, deterministic method, and appears to be a suitable method. Similar studies were conducted for the Corning Valor vials and SIOPlas vials filled on the respective filling lines.

A **product-specific** (b) (4) method was developed and qualified by the vendor for the CCIT of mRNA-1273 DP stored long-term at -20°C (-15°C to -25°C). This product-specific CCIT will be performed in lieu of sterility testing during stability studies.

Although Catalent is yet to submit its completed long-term CCIT results, the engineering study CCIT results provided indicate that the container closure system remains integral following the mRNA-1273 DP manufacturing process.

As this is a multidose vial and the drug product does not include a preservative, a microbial challenge study was performed to verify the diluted product was not conducive to microbial growth during the prescribed in-use storage period. The information provided supported that the drug product remained free of microbial growth during the in-use storage period. The testing was reviewed and found acceptable. Multi-dose functionality testing per (b) (4) was performed and found acceptable. Details can be found in the IND19745 drug product facility review for the Catalent Bloomington IN facility.

## **B. Process flow**

The process flow diagrams and descriptions for the manufacturing of the mRNA-1273 drug substance components were reviewed as part of the drug substance evaluation covered in the IND and the process flows in Moderna and Lonza facilities appeared adequate. Details can be found in the IND 19745 drug substance facility review memo. For the drug substance, critical manufacturing steps (e.g., (b) (4) ) are conducted under (b) (4)

mRNA-1273 manufacturing operations. (b) (4)

. The mitigation of cross contamination risk during mRNA-1273 drug substance manufacturing was reviewed and found acceptable (see the drug substance review memo under IND 19745 for the Moderna Norwood MA and Lonza Portsmouth NH facilities).

The process flow diagrams for the manufacturing of the mRNA-1273 drug product at the Catalent facility were reviewed as part of the drug product evaluation covered in the IND and the process flows appeared adequate. Details can be found in the IND19745 drug product facility review. The filling of the sterile drug product takes place under Grade (b) (4) conditions in (b) (4) filling lines at Catalent. Appropriate environmental monitoring is performed throughout the drug product manufacturing process. Mitigation of cross contamination during mRNA-1273 drug product was reviewed and found acceptable (see the drug product review memo under IND 19745 for the Catalent Bloomington IN facility).

### **C. Multiple product manufacturing**

All manufacturing areas used for mRNA-1273 DNA plasmid and drug substance are dedicated in the Moderna and Lonza facilities. Initially the production trains for mRNA-1273 drug substance will be dedicated and no mRNA-1273 will be produced in any other production area. Mitigation of cross contamination risks during manufacturing of mRNA-1273 DNA plasmid and drug substance were reviewed and found acceptable. Details can be found in the IND 19745 drug substance facility review memo for the Moderna Norwood MA and Lonza Portsmouth NH facilities.

Manufacturing areas used for mRNA-1273 drug product are multi-product areas. The filling lines are used for a number of FDA approved products and mRNA-1273 DP. Moderna stated under IND 19745 (SN 0070, section 3.2.A.1, *Facilities and Equipment*) that products manufactured at Catalent may share manufacturing areas and indirect or non-product contact multi-use equipment; however, product contact parts for mRNA-1273 DP are single-use, product dedicated, and disposable equipment.

New products entering the manufacturing facility undergo assessment for safety using Catalent's New Product Assessment (NPA) Policy (A-POL-03-01-004). The policy specifies that products outside the containment capabilities of the facility or that are deemed to be extremely toxic or posing a significant risk to personnel, equipment and validated cleaning methods may not be manufactured within the facility. Products requiring additional precautions may not be accepted until an additional risk assessment beyond the scope of the NPA procedure is completed. Catalent does not manufacture highly potent, live virus, beta-lactam antibiotics or cytotoxic drugs. Mitigation of cross contamination risks during manufacturing of mRNA-1273 drug product were reviewed and found acceptable. Details can be found in the IND 19745 drug product review memo for the Catalent Bloomington IN facility.

### **D. Critical equipment for drug substance and drug product manufacturing**

Most of the critical equipment (b) (4), etc.) with direct product-contact used to manufacture the mRNA-1273 from the DNA plasmid through the drug substance is dedicated or single-use and all equipment is qualified for use. Some of

the equipment (b) (4)

(b) (4) are shared at Scale A but dedicated at Scale B at the Moderna facility. Cleaning verification and monitoring were performed for the Scale A manufacturing process. Cleaning validation is currently on-going for the Scale B dedicated, re-usable equipment. Meanwhile, cleaning verification and monitoring are performed for Scale B equipment used currently in the manufacture of PPQ batches. Moderna submitted their Cleaning Validation Master Plan which was reviewed and found acceptable. At Lonza, only Scale B manufacturing is performed using product-dedicated or single-use equipment. The information was reviewed and found acceptable. Details can be found in the IND 019745 drug substance facility review memo for the Moderna Norwood MA and Lonza Portsmouth NH facilities.

All critical drug product manufacturing equipment is qualified for use. For the filling of the drug product, the product contact equipment is (b) (4), product dedicated single-use and disposable. The non-product contact large equipment is cleaned by (b) (4). The (b) (4) are decontaminated with (b) (4). Cleaning of equipment is performed per document A-SOP-21-01-006 *Sanitization of Equipment, Materials and Supplies for Primary Manufacturing*. The information was reviewed and found acceptable. Details of the information on the critical equipment can be found in the IND 19745 DP memo for the Catalent Bloomington IN facility.

#### **E. Aseptic process information and validation studies**

There are (b) (4) filling lines at Catalent that are currently used to fill mRNA-1273 – (b) (4) (b) (4). Catalent's Aseptic Process Simulation (APS) study requires at least (b) (4) acceptable runs using a (b) (4) strategy that covers all vial sizes and maximum fill durations. Additionally, (b) (4) vial (b) (4) (b) (4) are included in the APS studies. A minimum of (b) (4) media fills are planned for (b) (4). The latest APS study used the 10R 10mL vials, the same vials as those used for mRNA-1273, and there were no contaminated vials. In addition to the APS studies reviewed for the filling lines, the (b) (4) decontamination validation data and environmental monitoring during the APS studies were reviewed and found to be acceptable.

Details for (b) (4) filling lines and the information reviewed can be found in the IND 19745 drug product facility review memo for the Catalent Bloomington IN facility.

## **F. Drug product sterilization by filtration**

The mRNA-1273 drug product is sterile filtered via a (b) (4) sterilizing filtration (b) (4) (b) (4). For each mRNA-1273 batch, the filters are (b) (4) integrity tested and the (b) (4) filter is (b) (4) integrity tested. All filters passed integrity testing. The sterilizing filtration study results met the pre-defined process parameters and in-process control criteria, demonstrating that the filtration was successfully executed according to the manufacturing batch record and PPQ protocol.

The validation was performed for (b) (4) filters in contact with mRNA-1273 DP and was executed in accordance with (b) (4) (b) (4) and FDA Guidance for Industry, *Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice, September 2004*.

The bacterial retention qualification study, (b) (4) test results for all (b) (4) challenge filters met the firm's acceptance limit while testing under pre-defined worst-case conditions. The sterilizing filtration validation conducted by the filter manufacturer appears acceptable and details can be found in the IND 19745 drug product review memo for the Catalent Bloomington IN facility.

## **G. Sterilization and depyrogenation of equipment and materials (including CCS) used for final sterilized product**

Sterilization validation summaries for all equipment with direct contact with the final sterile product were provided and reviewed. The equipment and/or processes evaluated included: vial and stopper depyrogenation and sterilization, (b) (4) (b) (4) of equipment, (b) (4) sterilization of equipment and materials, (b) (4) decontamination, and (b) (4) sterilization. Data were reviewed and found acceptable. Details can be found in the IND 019745 drug product facility review memo for the Catalent Bloomington IN facility.

## **H. HVAC system, including area classifications, environmental monitoring, pressure differentials**

The HVAC system including pressure differentials, room classification, and environmental monitoring of all facilities responsible for the manufacturing of mRNA-1273 drug substance and drug product were reviewed and found acceptable for applicable processes at the respective process stages. All drug product filling operations occur in a Grade (b) (4) environment (b) (4). The environmental monitoring programs, including acceptance criteria and frequency, were reviewed and found acceptable. Details are in the IND 19745 review memos for the drug substance (Moderna Norwood MA and Lonza Portsmouth NH facilities) and drug product (Catalent Bloomington IN facility).

## **I. Multi-use areas -cleaning of the areas and change over procedures**

All manufacturing areas used for mRNA-1273 drug substance are dedicated, thereby mitigating the risk of cross contamination.

Manufacturing areas used for mRNA-1273 drug product manufacturing are multi-product areas, however the product contact equipment is product-dedicated, single use and disposable equipment. Campaign manufacturing is used and includes line clearance and area changeover procedures to mitigate the risk of cross contamination.

The disinfectant efficacy studies for each drug substance and the sanitization procedures for the drug product manufacturing facility were reviewed and found acceptable. Details are in the IND 19745 drug substance facility review memo for Moderna Norwood, MA and Lonza NH, the site visit report for Moderna, and the IND 19745 drug product facility review memo for Catalent Bloomington IN

## **J. Major utilities (water, compressed gases, etc.)**

The major utilities of all facilities responsible for the manufacturing of mRNA-1273 drug substance were reviewed and found acceptable. Details can be found in the IND 19745 drug substance facility review memo (Moderna Norwood MA and Lonza Portsmouth NH facilities) and the site visit report for the Moderna Norwood MA facility.

The major utilities including water for injection, purified water, clean steam, and compressed gasses of the facility responsible for the manufacturing of mRNA-1273 drug product are qualified and monitored. The critical utility information provided was reviewed and found acceptable. Details can be found in the IND 19745 drug product facility review memo for Catalent Bloomington IN.

## **K. The methods and controls to minimize cross-contamination including gowning procedures, personnel flow, waste disposal, automated access points, decontamination procedures**

Cross-contamination measures are in place at every drug substance and drug product facility, and include (b) (4) flow, progressive gowning, environmental monitoring programs, and changeover procedures.

As previously noted, all critical equipment with direct product contact used to manufacture the drug substance are dedicated or single-use and open operations are performed in either biological safety cabinets or laminar flow hoods. All mRNA-1273 drug substance facilities have environmental monitoring programs, progressive gowning protocols, validated utilities, and use qualified equipment with cleaning procedures in-place. Cross contamination measures at the drug substance facilities were reviewed and found acceptable. Details are in the IND 19745 drug substance

facility review memo (Moderna Norwood MA and Lonza Portsmouth NH) and the site visit report for the Moderna facility.

Drug product fill/finish is performed in a Grade (b) (4) environment and the aseptic processing is validated by aseptic process simulation studies. The manufacturing process has been demonstrated to consistently produce integral sterile vials. The mRNA-1273 drug product facility has an appropriate environmental monitoring program, progressive gowning protocols, validated utilities, differential pressure cascading for adjacent cleanrooms, and utilize single use, (b) (4) product contact equipment; large equipment (b) (4) etc.) have cleaning validation studies, validated vial depyrogenation process, and changeover procedures are in place. Cross contamination measures at the drug product facility were reviewed and found acceptable. Details can be found in the IND 19745 drug product facility review memo for the Catalent Bloomington IN facility.