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RESPONSE TO FDA REQUEST FOR INFORMATION, October 26, 2020

Introduction

Pursuant to the teleconference held on October 26, 2020, regarding FDA's request for additional facility information for the contract manufacturing facilities manufacturing mRNA-1273 Drug Substances (Lonza, Portsmouth) and Drug Product (Catalent, Bloomington), this document provides the Sponsor's responses to FDA's request for mRNA-1273 Drug Product (in **Bold**). Where the requested information is proprietary, reference to the specific DMF sections is included. An electronic copy will also be submitted directly to Obinna Echeozo, Randa Melhem, Tim Martin, Tony Lorenzo, and Sudhakar Agnihothram at the Agency's request.

FDA Request 1:

Please provide a description and qualification of the facility and equipment, relevant to mRNA-1273 manufacturing, and include HVAC description and qualification; room classifications, and pressure differentials; environmental monitoring program, environmental monitoring qualification, routine environmental monitoring and trending reports.

Sponsor Response to FDA Feedback for Request 1:

Catalent Facility Description and Qualification

mRNA-1273 Drug Product is manufactured in (b) (4) within the Catalent Indiana, LLC facility. Drug product areas are assigned a zone designation as listed in [Table 1](#) below.

(b) (4)

Air Handling Units have Installation and Operational Qualification and Environmental Monitoring Performance Qualification performed.

The objective of the Installation and Operational Qualification is to test the system in order to establish that:

- All critical components for direct impact systems are installed correctly, in accordance with design document requirements.
- The system is capable of operating within established limits and tolerances.

The objective of the Environmental Monitoring Performance Qualification is to collect viable and non-viable environmental data within the proposed classified areas to allow a determination of environmental quality and capability to be made so that an ongoing environmental monitoring program can be defined.

Air Handling Units (b) (4) support the manufacturing areas used in the mRNA-1273 manufacturing process. [Table 2](#) provides the Air Handling Unit validation references and User Requirements.

Table 2: Air Handler Unit Validation Overview

(b) (4)



Rooms controlled by each Air Handling Unit are provided in the Catalent (b) (4),
Section 3.2.A.1.2 Drug Product Systems, 3.2.1 HVAC Systems (b) (4)
(b) (4) [Table 3](#), Rooms Controlled by AHU. Room classifications which could be used for
mRNA-1273 manufacturing activities are provided in [Table 3](#).

Table 3: Manufacturing Rooms

(b) (4)



A complete list of manufacturing rooms is provided in the Catalent (b) (4),
Section 3.2.A.1.2 Drug Product Systems, 3.2.1 HVAC Systems (b) (4)
(b) (4) [Table 3](#), Rooms Controlled by AHU.

Equipment Qualification

(b) (4)



(b) (4)



Steam in Place (SIP) Cycle PQ

(b) (4)



[Table 4](#) summarizes cycle parameter settings that are utilized during validation and production runs. Validation cycles use reduced parameters to represent worst-case conditions.

Table 4: Worst Case PQ Parameters for Vial Configuration SIP

(b) (4)

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(b) (4)

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Environmental Monitoring Qualification

Parenteral manufacturing areas are validated per A-VAL-01-01-3227, Parenteral Manufacturing Environmental Monitoring Performance Qualification Protocol. The Environmental Performance Monitoring Performance Qualification (EMPQ) protocol collects viable and non-viable environmental data within the proposed classified areas to allow a determination of environmental quality and capability to be made so that an ongoing environmental monitoring program can be defined.

The Parenteral Manufacturing Environmental Monitoring measures and monitors that classified room maintain the pharmaceutical environment to the required grade. The environmental monitoring program is designed to provide information to operations, management, and quality personnel with regard to air and surface quality. Both viable and non-viable particles may affect sterile processes within the production environment and other background environments which support production.

The classified rooms are designed to maintain the specified grades in the Parenteral Manufacturing suite. (b) (4) air handling units provide heating, ventilation, and air conditioning to clean rooms. The HVAC systems maintains the temperature humidity, air flow, filtration, and pressure between rooms to maintain viable and non-viable particles below a controlled level. The filling operations are executed within a (b) (4), which is maintained to a (b) (4) and continually monitored during production with a PMS (Particle Monitoring System).

EMPQ data is measured at rest and in operation. At rest is the condition, after sanitization is performed to restore the area to a baseline state, where manufacturing equipment is present, but no personnel are present. In operation, for the purposes of EMPQ, is a state of activity in a room or an area in which operators are present and performing or simulating normal production activities.

The four elements to the EMPQ testing include surface monitoring, quantitative viable air monitoring, qualitative viable air monitoring, and total particulate monitoring.

Total particulate count must meet the maximum permissible levels criteria in [Table 5](#).

Table 5: Particulate Count Criteria

(b) (4)

The microbiological monitoring data must not exceed the criteria in [Table 6](#).

Table 6: Microbiological Monitoring Criteria

(b) (4)

The latest environmental monitoring performance qualification is documented in A-VPQ-00051-S, (b) (4) Renovation Environmental Monitoring Performance Qualification (EMPQ) Summary. The EMPQ data is provided in the Catalent (b) (4) (b) (4) Section 3.2.A.1.11 Microbiological Monitoring, 1 Facility/Standard Operational Environmental Monitoring Program.

The environmental monitoring program is performed per A-SOP-09-04-001, Environmental Monitoring Program and process qualification data. Results are recorded in the Laboratory Information Management System (LIMS).

The environmental monitoring program is designed to ensure that routine facility sanitization, standard manufacturing operations and gowning procedures are successful in maintaining facility environmental quality. Monitoring is conducted to ensure compliance of the manufacturing environment with established standards for viable surface, viable air and total particulate levels.

Routine sampling locations are chosen based upon review of the performance qualification results of the area, high contact/traffic areas, air flow visualization studies and consideration of critical areas and/or operations. This is completed by performing EMPQ of classified areas.

Defined control levels have been established for the classified areas. Exceeded levels are investigated according to procedure.

Table 7: Surface Viable monitoring actions levels (at rest and in operation)

(b) (4)



Table 8: Total Particulate action levels

(b) (4)



Details regarding the environmental monitoring program is provided in the Catalent (b) (4) (b) (4) Section 3.2.A.1.11 Microbiological Monitoring, 2 Routine Environmental Monitoring. Quarterly trending data is provided in the Catalent (b) (4) (b) (4), Section 3.2.A.1.11 Microbiological Monitoring, 1 Facility/Standard Operational Environmental Monitoring Program.

FDA Request 2:

Please list the manufacturing equipment used for the manufacturing of the DS and DP, indicating which equipment is product contact, single use, re-usable, shared and/or dedicated. Also, indicate which equipment has to be sterile prior to use, and whether the equipment is received sterile or sterilized in house. For the equipment sterilized in house, provide a description and qualification of the sterilizing equipment, and the validation of the sterilizing cycles and loads, to include description of the cycle parameters, loads, location of biological indicators and thermocouples (if applicable), acceptance criteria, results and deviations (if any).

Sponsor Response to FDA Feedback for Request 2:

Non-product contact equipment for the manufacture of the mRNA-1273 Drug Product is re-used and shared and includes the (b) (4) described in the Sponsor Response to FDA Feedback for Request 1 and the (b) (4).

All product contact manufacturing equipment used in the mRNA-1273 Drug Product manufacturing process are single use, product dedicated equipment. Sterile equipment is received sterile from the vendor.

Product contact manufacturing equipment include:

(b) (4)

FDA Request 3:

Please list and describe all the facility updates made related to the mRNA DS manufacture. For each update, provide the reason for change and describe the facility release criteria.

Sponsor Response to FDA Feedback for Request 3

Not Applicable to mRNA-1273 Drug Product manufacture at Catalent.

FDA Request 4:

Please provide detailed information for facility cleaning and re-usable/shared equipment cleaning, including but not limited to, description of the routine cleaning processes, frequency of cleaning; and summary reports of cleaning validation, acceptance criteria, results and deviations (if any).

Sponsor Response to FDA Feedback for Request 4:

Catalent Indiana, LLC defines the rationale and methodologies used during validation and/or verification of cleaning operations. The Cleaning Validation Master Plan, A-VAL-01-01-1611, outlines cleaning methods, the validation and verification approach and analytical methods used to successfully achieve a validated state for the cleaning procedures used.

Cleaning procedures are in place for each controlled area within the facility. The procedures detail the specific cleaning techniques, cleaning agents, used, the appropriate intervals of application, and the electronic tracking of sanitizations.

In addition, the cleaning solutions used in classified areas are appropriately qualified per A-SOP-09-01-011, Qualification of Sanitizing Solutions, are formulated by qualified personnel. Cleaning for Controlled Non-Classified, (b) (4) is performed per A-SOP-21-01-004, Sanitization of Classified and Controlled Areas within Primary Manufacturing Areas.

The sanitization scheduled utilized in the primary manufacturing areas for (b) (4) are provided in [Table 10](#).

Table 10: Sanitization Schedule for (b) (4)

(b) (4)



mRNA-1273 Drug Product manufacturing utilizes single use product contact equipment; therefore, equipment cleaning validation is not required.

FDA Request 5:

Please describe in detail the procedures for preventing contamination and cross-contamination to include, physical, temporal and procedural controls. Describe the campaign manufacturing strategy (if applicable).

Sponsor Response to FDA Feedback for Request 5:

As Catalent Indiana, LLC is a multi-product manufacturing site, products may share manufacturing areas and indirect or non-product contact multi-use equipment. Formal processes which include: temporal segregation, physical segregation, and validation/verification of cleaning procedures, area clearance and sample testing are in place to ensure that any potential carryover between products meets pre-defined safety limits based on Maximum Allowable Carryover (MAC) calculations for active products.

Catalent Indiana, LLC utilizes two types of clearances (Manufacturing and Quality Assurance) for pre and post production activities, as applicable. These clearances take the form of a full clearance (between two different products) or an abbreviated clearance, utilized during a campaign. Clearances are an element of the change-over process and support the practice of enforcing that only one product can be filled at a time within a defined area.

In order to reduce the potential for cross-contamination between drug products, client dedicated, or disposable equipment is utilized whenever appropriate. In common areas (b) (4) (b) (4) change-over procedures emphasize the proper clearing of these areas between the manufacture of different drug products.

A detailed description of the change-over and cross contamination prevention measures is provided in the Catalent (b) (4), Section 3.2.A.1.4 Cleaning Validation, Section 2 Procedures to Prevent Cross Contamination.

FDA Request 6:

For Catalent, please submit Aseptic Process Simulation/Media Fill summary report to qualify the line/process for filling of mRNA-1273 DP using the (b) (4).

Sponsor Response to FDA Feedback for Request 6:

(b) (4)



Media fill details are provided in Catalent (b) (4), 3.2.A.1.16, Media Fill Validation – (b) (4) Section 3 Initial Media Fill Qualifications and Section 4 Routine Media Fills – Vial.