From: Wonnacott, Keith
To: Giordano, Erica
Cc: Riggins, Cindy; Bobo, Qiao; Melhem, Randa
Subject: RE: BL 125646/0 DMPQ Information Request
Date: Wednesday, March 15, 2017 2:28:37 PM
Attachments: 7008911_ANSW_MC_840_3.pdf
Sensitivity: Confidential

Dear Erica,
Attached are the responses to the CMC information request received on February 27, 2017. There a total of 71 documents: one ANSW document and 70 appendices. The ANSW document is attached to this email. The attachments will come in 8 separate emails to help ensure that the file size is not too large for delivery. We will follow up with a BLA submission through the gateway of these documents.

Keith Wonnacott

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Monday, February 27, 2017 7:54 PM
To: Patel, Manisha
Cc: Chapman, Jonelle; Riggins, Cindy; Bobo, Qiao; Melhem, Randa
Subject: BL 125646/0 DMPQ Information Request
Sensitivity: Confidential

Good evening,

Please provide a response to the information request below by noon on March 15, 2017.

HVAC/Environmental Monitoring

Please list the AHUs (air handling units) at the Novartis Morris Plains manufacturing facility, and the respective suites/modules and ancillary areas they service, and the most recent requalification report(s). Please also list whether the ventilation is accomplished by single pass or recirculated air, and justify your response.

You reported the cleanroom environmental monitoring performance qualification (EMPQ) was successfully performed under static and dynamic conditions for Modules (b) (4) Please clarify if these are the only modules that will be used for the production of CTL019.

Please provide the protocol and summary report (s) for dynamic environmental monitoring performance qualification studies. Please include a description of activities performed during dynamic operations and indicate whether 'worst case' conditions were assessed.

You reported that the environmental monitoring program included surface, air viable and air nonviable particulates. Please describe the environmental monitoring program, including diagrams depicting sampling locations (with justification) and frequency of sampling as well as the acceptance criteria for the different area classifications. Please provide a comparison of environmental monitoring performed during qualification activities, routine dynamic environmental monitoring, and static environmental monitoring. Please provide the environmental monitoring report documenting the results of environmental monitoring during the manufacturing of the conformance lots and the aseptic process simulation lots.

Equipment Qualifications

You reported that a "comprehensive equipment qualification program has been established at the Novartis Morris Plains manufacturing facility which includes installation, operational and performance qualification activities."
Please describe and provide the qualification reports or detailed summaries for the following equipment to demonstrate the functionality and suitability for their use during the manufacturing of CTL019. Also please provide the validation of the cleaning procedure and the routine cleaning/sanitization procedure of the following equipment (if applicable).
Thawing device (leukopheresis bags)
Bag rotator
Centrifuge (refrigerated)
Closed automated cell separation system
Conical Tube Magnetic Bead Separator
Flatbed Bag Magnetic Bead Separation System
CO_2 incubators
Autologous Blood Recovery System
Rocking bioreactor
Controlled rate freezer
LN2 freezer
Biosafety cabinet

Please list the number of modules and work stations at the Morris Plains facilities, and their respective uses.

Segregation/ Chain of Identity

You stated that you would be manufacturing both licensed and IND products in the facility. Please provide your segregation policy between the licensed and unlicensed products, and provide studies and/or risk assessments to support your segregation program.

There will be several leukopheresis units (different patients) processed at the facility at the same time. Please describe the procedures in place, and their qualifications to maintain the chain of identity from the Apehersis center, to receipt at Morris Plains facility to different manufacturing steps (including QC testing), final product (including release testing), and then shipment to the clinic.

You reported that you implemented the (b) (4) system for the scheduling and monitoring of the process, and that (b) (4) is integrated with the SAP system at the Morris Plains site. Please provide a detailed description of the (b) (4) system, the user requirements, and the validation studies and their results to demonstrate suitability of the (b) (4) for its intended use, and for compliance with user requirements.

Process Validation

. Each patient lot is a separate manufacturing operation with several manual manipulations and incubation steps over a span of (b) (4). Have you performed capacity studies (actual or simulated) to determine the number of lots that the facility/equipment/QC and personnel can handle and sustain per day, week, etc…? Please provide a detailed description and results.

. You reported that three successful PPQ lots were manufactured to qualify each of the (b) (4)

pathway and (b) (4) pathway manufacturing processes. Please clarify which modules (and work stations) were used, and whether (b) (4) through the whole manufacturing process of that lot. Please clarify, and describe the cleaning and line clearance procedure for the BSC, and whether it is performed after every step, every day, etc.

. Please specify the incubators used for the manufacturing of the conformance lots, and clarify whether lots manufactured concurrently can be incubated in the same incubator. Please explain and describe the segregation of the lots in incubators.

Aseptic process validation (APV)

. You reported that the aseptic process validation is performed for both CTL019 manufacturing process and for the cell culture media preparation process, every (b) (4) , ***in the manufacturing module***. It is not clear whether you are referring to a specific module, and the number of BSCs involved in the (b) (4) APV for each process (to simulate worst case conditions). Please explain and justify your response.

. You reported that the initial APV for the CTL019 was conducted in Module (b) (, and included (b) (4) work stations (out of (b) (4) work stations) for that module as routine production of CTL019 uses up to (b) (4) BSC (each BSC in a work station). You explained that (b) (4) work station (BSC with its ancillary equipment) was used to simulate the CTL019 process by using (b) (4) and the other (b) (4) work stations were used to simulate the CTL019 process using (b) (4) , to create a challenge operations condition in terms of personnel movement and particulate generation during APV. Each APV run in each of the (b) (4) work stations was completed in (b) (4) utilizing (b) (4) of personnel due to the length of the process. You also reported that the validation process included (b) (4) validation runs: (b) (4) run per work station on (b) (4) separate days.

Please clarify if Module (b) (4 is the only module that will be used for the production of CTL019. If other modules are used, please explain your APV strategy for qualification of those modules, and justify your response.

You reported that during APV, the incubation times were reduced; and you added that worst case incubation times were evaluated using (b) (4) in a separate study conducted prior to this APV study, and that all results were compliant. Please provide the protocol and summary report for that study.

You reported that during APV you sampled after each step and that the final container was sampled and tested for sterility. Please clarify whether the final container (filled with (b) (4) was incubated (and assessed for absence of growth, followed by growth promotion studies), to demonstrate the validity of the aseptic process, and justify your response.

You also reported the APV for cell culture media preparation was performed in (b) (4) work stations of Module (b) (4 Please clarify if Module (b) (is the only module used for the preparation of cell culture media. If other modules are used, please explain your APV strategy for qualification of those modules, and justify your response.

Continued Process Verification

. You provided in report *PVP5135-6B, Continued Process Verification Plan: CTL019 Product* links to several documents, however all the links go to the Reference section of the same document. Please submit the referenced documents.

Please confirm receipt of this requests and let me know if you have any questions.

Thank you,

Erica Giordano
Regulatory Project Manager

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