

From: Sweeney, Colleen
Sent: Tuesday, August 02, 2016 2:21 PM
To: Margaretten, Nadine (nadine_margaretten@merck.com)
Cc: Steele, Matthew; Khurana, Taruna
Subject: RE: 125592/0

Dear Dr. Margaretten,

We have the following requests for additional information regarding your biologics license application (BLA):

1. We note that following the (b) (4) of the source material, the culture is (b) (4) in the cultivation (b) (4). Please provide data to support this hold time.
2. In Section 3.2.S.2.3, Control of Materials for the drug substance (DS), Table 14 lists the product contact materials used in the DS manufacturing process. We have the following items:
 - a. Please indicate which product contact materials are disposable.
 - b. Please clarify if the (b) (4) are re-used. If so, please provide information on the re-use criteria, such as (b) (4).
3. Please provide a summary of the equipment qualifications for the (b) (4).
4. The container closure system used for the drug substance consists of an (b) (4). We have the following items:
 - a. Please confirm that the same container closure system is used for storing the in-process material (b) (4). If not, please provide detail information for the container closure system used for storing the (b) (4).
 - b. Please clarify if the container and (b) (4) are single use or re-used. If re-used, please provide a cleaning validation summary for the container and (b) (4), including if any preliminary cleaning of the containers and (b) (4) is performed at Catalent Pharma Solutions, prior to returning to (b) (4).

- c. Please indicate if the (b) (4) containers and (b) (4) are supplied as “ready-to-use” from your vendor. If so, please indicate how the containers and (b) (4) are assessed for cleanliness prior to use. If not, please indicate how the containers and (b) (4) are prepared for use.
5. The Drug Substance manufacturing process includes a (b) (4)
[REDACTED]
We note that in Section 2.3.S., Table 19 indicates the (b) (4)
[REDACTED] The DS manufacturing flowchart does not indicate when the (b) (4) is performed. Please clarify if any in-process (b) (4) monitoring is performed. If not performed, please provide a justification and risk assessment for not monitoring (b) (4) during production.
6. Please describe the receipt and acceptance process for the in-coming drug substance upon receipt at Catalent Pharma, including if any (b) (4) is performed.
7. In Section 3.2.P.2.5 (Microbiological Attributes), you state that several steps have been introduced to ensure the microbiological quality of the (b) (4), drug product (b) (4), and the freeze-dried drug product (DP) during the manufacturing process. Please provide validation data to support the following process parameters used to reduce or slow potential microbial proliferation:
- (b) (4)
[REDACTED]
8. The container closure system for the Drug Product, i.e., House Dust Mites (HDM) tablet is an all-aluminum blister card sealed with a paper/foil laminate lidding foil. An in-process check includes a visual inspection of the (b) (4). Please address the following items in your response:
- a. Operator training / qualification for performing the visual inspection;
 - b. Design of the blister card including the size of the (b) (4) and minimum seal distance between blisters; and
 - c. Validation summary for (b) (4) quality and peel-ability of the blister cards.

9. Please provide validation data for the (b) (4) test method used to detect defects in the seal integrity of the all-aluminum blister cards. Please address the following items in your response:
- Please clarify if your package has adequate (b) (4) characteristics to test using the (b) (4) method.
 - Please clarify if the (b) (4) is standardized. In addition, please clarify (b) (4).
 - Please indicate the amount of (b) (4) an operator would be able to visually recognize.
 - Please clarify if you are using a positive control ((b) (4)). In addition, please clarify if you have challenged the procedure to determine what (b) (4) operators can visually recognize.
 - Please clarify if you challenge the method regularly to confirm its ability to detect defects.

10. Please provide the operational and performance qualification protocols and a summary of the qualification results for the following equipment:

- (b) (4)

11. Catalent Production Line (b) (4) includes (b) (4) freeze driers (b) (4). Please indicate if the (b) (4) freeze driers are of similar design and operating principle.

12. In Section 3.2.A.1.6, Table 2 lists the Production Line (b) (4) freezer drier operational qualification acceptance criteria and results for Freeze Drier (b) (4). Please provide the product temperature and ramp rates for each phase of the lyophilization cycle.

13. Please indicate if any deviations occurred during the process validation of the drug substance or drug product. If so, please provide a summary of the deviation, assignable root cause, and corrective actions.

14. Please provide a summary of the equipment qualifications for the (b) (4)

Please submit the above information as an amendment to STN 125592/0.

Thank you,

Colleen Sweeney R.N., M.S.

Captain, USPHS

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