
From: Khurana, Taruna
Sent: Wednesday, September 14, 2016 10:37 AM
To: nadine_margaretten@merck.com
Cc: Steele, Matthew (Matthew.Steele@fda.hhs.gov); Sweeney, Colleen
Subject: STN 125592/0 CMC-IR (9.14.16)

Dear Dr. Margaretten,

Please see the following information request regarding Chemistry Manufacturing and Controls of your BLA. If possible, please reply by the first week of October.

Source Material

1. We notice that (b) (4) is not included as release specification for Der pte and Der far (b) (4).
The stability data included in the BLA amendment submitted on August 5, 2016 show increasing trend in (b) (4). Increase in (b) (4) can cause increased (b) (4) of the (b) (4). Please include (b) (4) as release test for Der pte and Der far (b) (4) source material.

Drug Substance

2. Section 3.2.S.2.6.7, Justification of acceptance criteria and PARs for the commercial scale production process, Table 3 -Process Parameters for the HDM Der far and Der pte (b) (4) process has (b) (4) indicated as non-critical parameter. (b) (4) outside the range can affect (b) (4). Please comment and amend the critical parameter table.
3. In section 3.2.S.2.6.7 you have (b) (4). Please clarify this statement and indicate the outcome of a batch that does not pass the acceptance criteria for (b) (4).
4. Please indicate qualification procedure for each new batch of (b) (4).
5. Please clearly indicate the method ((b) (4)) currently used for determining the (b) (4) of the DS and DP batches during release and stability testing.
6. Please provide qualification protocol and data for the drug substance (b) (4) tests.

Drug Product

7. In section 3.2.P.3 Drug Product Manufacturing Process you have that (b) (4) is responsible for the storage. Please clarify.
8. Please indicate the amount of drug substance used during commercial scale manufacturing of a drug product batch.
9. In section 3.2.P.5, control of drug product, we notice that drug product batches are not tested for (b) (4). Assessing (b) (4) in comparison to in house reference

material is indicative of compositional consistency among the batches and overall quality of the final product. We suggest you include (b) (4) test for the drug product.

10. Please provide qualification protocol and data for drug product microbial enumeration tests.
11. Please provide 36 month stability data for pilot scale drug product batch (b) (4).
12. Please provide additional stability data for Process Validation batches and additional commercial scale batch (b) (4) . The stability for PPQ batches was initiated on April 30, 2014 and batch (b) (4) was place for stability test on April 15, 2013
13. Please provide Certificate of Analysis issued by Catalent, UK for the final drug product.
14. Please provide certification for gelatin from the supplier.
15. Please provide Certificates of Analyses for mannitol and sodium hydroxide.

Thank you
Taruna

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