Merck BLA 125473- Information Request

Drug Substance

3.2.S.2.2- Description of Manufacturing Process/Process Control

1. Section 2.0, Processing of source material- (b)(4)

2. Section 2.0, Processing of source material- (b)(4)

3. Section 2.0, Processing of source material- (b)(4)

3.2.S.2.3- Control of Materials

4. We note that the pollen is tested (b)(4) for (b)(4) . However, it is not clear from your descriptions if more than one batch or lot of pollen may be harvested from a field in a year. Please clarify. If more than one batch or lot is harvested from a field in a year, then we request that each individual harvest be tested for (b)(4) . In addition, please specify which methods, compendial or otherwise, are used for testing these materials.

5. In section 2.3, (b)(4) testing of source pollen- you provided testing data for (b)(4) for pollen batches harvested between 2003 and 2007. Please provide the same information and data for the pollen batches harvested after 2007.

6. Attachment 1 of this section is a representative Certificate of Analysis (CoA) from source material vendor (b)(4) We note that no expiration date is indicated on the CoA. Please explain why no expiration date is provided on the CoA and specify if an expiration date is assigned to the pollen source materials. In addition, please indicate if stability studies are performed in support of the expiration date and provide any available data.

7. Please provide the SOPs for the tests indicated in CoA provided by (b)(4) .

8. We note that per your description; ALK Abello A/S accepts source materials from (b) (4) based in part on the CoA and in part on some in-house testing. ALK Abello A/S should have a vendor auditing program in place, especially if results are accepted by CoA. Please provide a description of ALK Abello A/S' vendor qualification program and specify if on-site auditing is performed.

9. Please explain the process used by ALK Abello to track raw materials from receipt through the quarantine, release and storage process. In addition, if an automated system is used, please provide an overview of this system.

10. In Section 3.0- you indicate that a (b)(4) is evaluated based on certificate of analysis from supplier. Please provide a CoA for the (b)(4) .

3.2.S.2.4- Control of Critical Steps and Intermediates

11. Table 1 in section 1.0 lists all of the operating parameters and process controls for the DS manufacturing process. (b)(4) are considered as critical steps through the entire manufacturing process of the DS. We do not agree with your classification of most of the operating parameters of the DS production process as "non-critical". Further discussion on these classifications will be necessary.

12. (b)(4) Please explain.

3.2.S.2.5- Process Validation and Evaluation

13. Please address the following with respect to the values listed in Table 5, Validation Results Process Parameter Conformance SCH 697243 (batches (b)(4)):

    a. The Proven Acceptable Range (PAR) for the (b) (4) Please provide validation data supporting the PAR for this step.

    b. The PAR for (b) (4) Please provide validation data supporting the PAR for this step.

c. (b)(4) . Please provide validation data supporting the (b)(4) .

d. The PAR for (b) (4) Please provide validation data supporting the PAR for this step.

14. Please provide SOPs for the preparation, qualification, control and storage conditions for your in-house reference materials (IHR's). In addition, please indicate what the expiration date is for your IHR materials.

3.2.S.2.6- Manufacturing Process Development

15. (b)(4) Please provide the validation studies supporting this (b)(4)

16. Please provide process validation studies and resulting data for the (b)(4) step.

17. You indicate that an analytical study was conducted to compare the (b) (4) of DS. Analytical tests were performed in support of this study. Please provide the analytical testing data from this comparative testing; (b)(4) .

3.2 S.4- Control of Drug Substance

18. Please specify how often you (b)(4)

19. Please provide specifications for the (b)(4) .

20. In section 3.2.S.4.2, (b)(4) Figure 1 is a typical result from (b)(4) . Please provide the figure for the DS sample for comparison.

21. (b)(4)

(b)(4)

please provide supporting data.

23. In Section 10.0, Reporting results, we note that (b)(4) . Please explain.

3.2.S.4.3- Validation of Analytical Procedures

24. (b)(4) ". Please provide this guide for review.

3.2.S.4.4- Batch Analysis

25. We note that different types of batch numbers are used for the DS. For example, in Table 3 ((b)(4) Batches of SCH 697243 Drug Substance) a batch is designated as (b)(4) while another batch is designated as (b)(4) . Please explain why different batch numbers are used.

3.2.S.7- Stability

26. You have proposed not to include (b) (4) (b) (4) batches. Please explain your rationale for excluding these tests.

Drug Product

3.2.P.2.3- Manufacturing Process Development

27. In Table 1 we note that either (b)(4) Please specify which process you intend to use for (b)(4) for commercial scale production batches.

28. Please provide the procedure used for (b)(4) of DS.

29. In table 14, Effect of Freeze Drying Conditions on Dried Tablets, we note that frozen and dried tablets from batch (b)(4) (active) were not tested for moisture content, and that tablets from freeze dryer loads (b)(4) were not tested for appearance. Please explain why this batch was not tested as intended.

3.2.P.3.5 Process validation and /or evaluation

30. In table 4 you indicate that process validation batches comply with the (b)(4) , however you have not provided any supporting data. Please provide the (b)(4) data for all of process validation batches.

31. In table 5- the moisture content of all of the process validation batches is well below (b)(4). Please consider modifying your release and shelf life specification for moisture content based on water content data from your process validation batches.

3.2.P.4 Control of excipient

32. In Appendix 1 Certification for gelatin from (b)(4) has been provided but your gelatin is obtained from (b)(4) Please provide certification for gelatin from (b)(4)

33. Please provide Certificates of Analysis for both mannitol and sodium hydroxide.

3.2.P.5.2 Analytical procedures

34. In your interpretation of the method for the FDA ELISA, Section 4.0 reagents, you use (b)(4) is as a wash and dilution buffer. Per the current FDA competition ELISA procedures; the wash solution should be PBS containing 0.05% Tween-20. Please align your wash and dilution buffer composition to comply with the FDA standard method of competition ELISA.

35. For the (b)(4) by (b)(4) you use (b)(4) . Please indicate why you use (b)(4) and describe your method (b)(4) .

3.2.P.5.3 Validation of Analytical Procedures

36. For validation of the CBER ELISA method you have only included a summary of the validation parameters. Please provide complete data from the batches that were tested during validation of this assay. Please specify which versions of the CBER ELISA method and optimization methods are used.

3.2.P.5.4 Batch Analysis

37. We note that different types of batch numbers are used for DP batches. For example in Table 1 of this section the batch numbers indicated are (b)(4) . Please explain the difference in these numbers.

3.2.P.5.6 Justification of Specifications

38. Please provide information on the modifications you added to (b)(4) during disintegration testing.

3.2.P.8 Stability

39. You used three PV batches from (b)(4) for your stability studies. In this sequence, batch number (b)(4) is missing. Please specify the outcome of the missing batch.

40. Section 2, Batch Information – you indicate in the Table 1 footnote that a second accelerated stability study was performed to include FDA ELISA assay since it was inadvertently not performed in the original study. Please explain why the FDA ELISA assay was not performed during first accelerated stability study that was initiated on all three batches ((b)(4)) on June 4, 2008.

41. You propose not to include microbiological examination for specified microorganisms in your future stability protocol. You have not provided sufficient information to assess whether this proposal is acceptable. Please provide your rationale for not including this test during stability studies.

42. Please provide 36 month stability data for PV batches stored under real time conditions.

3.2. R Regional Information

43. The CoA from Catalent Pharma Soutions lists the date of manufacture as December 14, 2009 and the expiration date as 11, 2013. Please comment on the following:
    a. The indicated expiration date of "11, 2013" is incomplete. This is not a complete expiration date. Please explain why there is not a complete expiration date on the CoA.
    b. Based on your proposed expiration dating of 36 months, the expiration date should be in 2012 not 2013 as indicated in the CoA. Please comment.
    c. Please indicate which firm is responsible for assigning the expiration date to the blister pack.
    d. Please explain how you define the Date of Manufacture. This is the date from which the expiration should be calculated.