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From: Rivers, Katie
Sent: Friday, November 08, 2013 10:15 AM
To: 'Greenfeder, Scott'
Cc: Valenti, Elizabeth
Subject: Information request for STN125748/0

Dear Scott,

We have the following information request for your BLA, STN125478/0:

Drug Substance

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

1. (b) (4)
2. (b) (4) .
3. (b) (4)
4. (b) (4)

3.2.S.2.3 - Control of Materials

5. (b) (4)

1 page determined to be not releasable: (b)(4)

3.2.S.2.5 - Process Validation and Evaluation

13. Please provide data obtained from the process design phase that were used for defining proven acceptable ranges indicated in Table 5- Process Performance Qualification (PPQ) Results Process Parameters Conformance.

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

(b) (4)

(b) (4)

3.2.S.4.3 - Validation of Analytical Procedures

21. Validation of (b) (4), Section 4.0, Robustness- You indicate that the variations in the concentration of *Ambrosia artemisiifolia* were applied. Please specify the concentration range of (b) (4) tested during validation of (b) (4).

3.2.S.4.4 - Batch Analysis

22. We note that different types of batch numbers are used for the DS. For example, in Table 1 (List of development, clinical, stability and PPQ batches), one batch is designated as (b) (4) while another batch is designated as (b) (4) and another as (b) (4) Please explain why different types of batch numbers are used.

23. (b) (4) data are missing for batch (b) (4). Please provide these data.

24. In the footnote for Table 6 you indicate that batches (b) (4), (b) (4) were not used in manufacturing of DP. Please explain what these batches were used for.

3.2.S.4.5 - Justification of Specification

25. Section 3.0, Potency, Major Allergen Activity- The (b) (4) In Table 4, you indicate that the tolerance limit is derived from the (b) (4) data obtained from (b) (4) Table. However, we note that all of the batches in Table 4 have Amb a 1 Units of less than (b) (4). Please explain how you defined the Amb a 1 interval limits and provide any supporting data analysis.

26. Section 6.0, Microbiological Enumeration- Please provide (b) (4) data for all (b) (4) batches.

3.2.S.5 - Reference Standards or Materials

27. You proposed a (b) (4) expiration date for the current IHR material (b) (4) based on an on-going stability program on (b) (4) IHR (b) (4). However, you have not provided any data supporting the (b) (4) expiration date. Please provide stability data in support of your proposed expiration date of the IHR.

28. Please provide your complete SOPs for the preparation, qualification, and control of your IHR materials.

3.2.S.7 - Stability

29. The commercial scale batches placed under stability study (b) (4) were not tested for (b) (4). Please explain why these batches were not tested as intended.

30. Only (b) (4) stability data for both the (b) (4) assays have been provided for (b) (4) commercial scale batches (Tables 15, 16, and 17). Please provide additional stability data for these DS batches.

31. You have proposed not to include (b) (4) profiling for your post approval stability batches. Please explain your rationale for excluding these tests.

32. Please provide stability data for the (b) (4) PPQ batches listed in Table 11.

Drug Product

3.2.P.3 - Manufacture

33. Section 3.2.P.3.2, Batch Formula- You indicate that the range of (b) (4) for each commercial scale batch of (b) (4) whereas, in the footnote to Table 1, you indicate that (b) (4) are typically used. Please specify the exact range of (b) (4) used during commercial scale DP batch manufacturing.

3.2.P.3.5 - Process Validation and/or Evaluation

34. In Table 5 the moisture content for all of the batches is well below (b) (4). Please modify 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

35. Please provide Certificates of Analysis for mannitol, sodium hydroxide, and gelatin

3.2.P.5.4 - Batch Analysis

36. Table 6, Analysis for Potency of Commercial Scale and PPQ batches- (b) (4) data are not provided for commercial scale batches (b) (4). Please provide (b) (4) data for these commercial scale batches.

3.2.P.8 - Stability

37. (b) (4) commercial scale batches (b) (4) were used for your stability studies. In this sequence, batch number (b) (4) is missing. Please specify the outcome of the missing batch.

38. Section 3.2.P.8.2, Post Approval Stability protocol/stability commitment, Table 1- We note that the identity test and test for absence of specified microorganisms is not included in post approval stability protocol. You have not provided sufficient information to assess whether this is acceptable. Please provide your rationale for not including these tests on stability.

39. We note that identity test by (b) (4) and the absence of specified microorganisms were not performed during stability studies for any of the stability batches. Please provide your rationale for not performing these tests during the stability studies.

40. Section 3.2.P.8.3, Stability Data, Table 9, Test Program for Long Term Testing of Pilot Scale Stability Batches- The test for absence of specified microorganisms was not included at the (b) (4) time point. Please provide a rationale for not including this test at (b) (4) .

41. Section 3.2.P.8.3, Stability Data, Table 13, Test Program for Long Term Testing of PPQ Batches- The microbial quality test for absence of pathogens is performed only at (b) (4) of the stability (b) (4) Please explain why this test is not performed at time points other than (b) (4)

42. Section 3.2.P.8.3, Stability Data, Table 16 (b) (4) You have not provided data for absence of specified microorganisms for these lots. Please explain why the test was not included during these stability studies. Please include this test in your on-going stability studies.

3.2. R - Regional Information

43. Please provide a Certificate of Analysis from Catalent Pharma Solutions for the drug product.

Other

44. Please submit a draft Lot Release Protocol.

Please let me know if you have any questions.

Thank you,
Katie

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