(System Info - 285047 SMITH MICHAEL 08/29/2014 15:31:12 SMITHM)

RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA Submission ID: 125549/0 Office: OVRR

Product:
Meningococcal Group B Vaccine

Applicant:
Wyeth Pharmaceuticals Inc.

Telecon Date/Time: 29-Aug-2014 02:57 PM Initiated by FDA? Yes

Telephone Number:

Communication Categorie(s):
1. Information Request
2. Other - CMC IR's

Author: MICHAEL SMITH

Telecon Summary:
CMC IR's

FDA Participants: Mike Smith, Drusilla Burns, Ted Garnet and Ram Naik

Non-FDA Participants: Carmel Devlin

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

See e-mail below:

From: Smith, Michael (CBER)
Sent: Friday, August 29, 2014 2:57 PM
To: Devlin, Carmel (Carmel.Devlin@pfizer.com)
Cc: Burns, Drusilla L.; Garnett, Theodore; Naik, Ramachandra
Subject: STN 125549: IR on CMC issues

Carmel,

The review team has the attached information requests (IR's) on CMC issues. Please confirm receipt of these IR's and let us know when you anticipate submitting Pfizer's responses to the BLA.

Regards,

Mike

Mike Smith, Ph.D.
CDR, U.S. Public Health Service
Regulatory Project Manager
U.S. Food and Drug Administration
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See contents of attached PDF below:

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCT APPLICATIONS

Date: August 29, 2014

Pages: 14

To: Carmel Devlin
Senior Director, Worldwide Regulatory Strategy
Pfizer Inc.
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From: Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Point of Contact: CDR Mike Smith, Ph.D.
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10903 New Hampshire Ave., White Oak Bldg. 71
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STN#: 125549/0

Product: Meningococcal Group B Vaccine

Subject: CBER information request regarding Chemistry, Manufacturing and Controls (CMC), issues

Drug Substance:

1. ----------(b)(4)----------.

2. ----------(b)(4)----------.

3. ----------(b)(4)----------.

4. ----------(b)(4)----------.

   a. ----------(b)(4)----------.

   b. ----------(b)(4)----------.

5. ----------(b)(4)----------.

   a. ----------(b)(4)----------

6 pages redacted (b)(4)

----------(b)(4)----------
----------.

Drug Product:

20. Filter Extractable Studies (Section 3.2.P.3.5) were performed only on ----------(b)(4)----------. Please provide a comparison of all filters used during the manufacture of drug product. Please provide filter extractable studies for all filters used during drug product manufacture. Alternatively, provide your justification that the chosen filter is representative of all the filters used during drug product manufacture

    a. You have provided a summary of the extractable results in Section 3.2.P.3.5.3. However, you have not included the identity of the residues. Please provide the extractable study report. This report should include details on how the study was performed, the identity of the residues extracted, and the acceptance criteria for these residues.

    b. You have not provided data for leachables on the filters. Please provide leachable data for your filters used during manufacture of drug product.

21. You have proposed a ----------(b)(4)----------(b)(4)----------. You state in Section 3.2.P.2.3.1.1.1 that the "…proven acceptable range (PAR) for (b)(4) storage temperature was determined to be between ------(b)(4)-------." You also state that you have a robustness study that "suggests that (b)(4) quality attributes -------(b)(4)------- remained unchanged ----------(b)(4)--------- at these temperatures." Please provide data to support a ----------(b)(4)---------- at the temperature limits that you propose as your proven acceptable range (between ------(b)(4)------). Please clarify at what temperature ---------(b)(4)---------- will be stored at in the Pfizer, ---(b)(4)--- facility.

22. You state in Section 3.2.P.2.3.1.1.2 that the ----------(b)(4)---------- time at Pfizer, (b)(4) is -------(b)(4)--------. You state in Table 3.2.P.2.3-6 that the proven acceptable range (PAR) for ---(b)(4)------- ----------(b)(4)----------. Please clarify and provide data to support the validated ----------(b)(4)----------. In addition, please provide the ----------(b)(4)---------- used to manufacture your commercial scale lots at your Pfizer, ---(b)(4)--- facility.

23. You state in Section 3.2.P.2.3.1.1.2 that the ----------(b)(4)----------. Please clarify if -----(b)(4)------ at ----------(b)(4)----------. You have provided data to support the (b)(4) time at ----------(b)(4)----------. If this is a ------(b)(4)----- time, please provide data to support the ------(b)(4)------ time.

24. We note in Table 3.2.P.3.5-1 “Drug Product Manufacturing Process Validation Lots” that you used ---------(b)(4)---------- AlPO4 lots in the manufacture of the three drug product validation lots. We prefer process validation lots be manufactured with three different lots of starting material. In lieu of using three different lots of AlPO4, please provide the batch genealogy for all drug product lots manufactured post process-validation.

25. The following comments relate to the control of AlPO4 (Section 3.2.P.4).

    a. You propose an aluminum concentration release specification for AlPO4 of ----(b)(4)----. This specification is based on (b)(4) batches of AlPO4 ----------(b)(4)---------- and the limits were based on (b)(4) sigma limits. Please revise your specifications to reflect batches ----------(b)(4)-------- and base the limits on (b)(4) sigma limits.

    b. You propose a release specification for ----------(b)(4)---------- based on batches produced in -----(b)(4)----- based on (b)(4) sigma limits. Please revise your specifications to reflect batches manufactured at ------(b)(4)---------- and base the limits on (b)(4) sigma limits. In addition, please include ----------(b)(4)----------.

    c. ----------(b)(4)----------.

26. The following comments relate to the Purity Determination of Drug Product by ---(b)(4)--- (Sections 3.2.P.5.2 and 3.2.P.5.3).

    a. Please provide your detailed procedure for the determination of purity in drug product.

    b. The procedure includes the preparation of an appropriate control by ----------(b)(4)----------. Please provide detailed information on the control material to include manufacture, qualification, storage, and expiry.

    c. The method as described does not include measurement and acceptance criteria for ----b(4)---------- ------- performance in terms of –b(4)---------- as well as –b(4)---------- should be part of acceptance criteria for the assay. –b(4)---------- should include the degradant compounds intended to be monitored by this procedure. Please incorporate these additional system suitability criteria into your procedure.

    d. The percent purity is calculated as ----------(b)(4)----------

----------(b)(4)----------. We do not concur with this proposal. Please include ----------(b)(4)----------, in your calculation of purity.

e. You have included data for % purity in your evaluation of repeatability, intermediate precision, and linearity. Please include data to evaluate integration of the following in these studies as well: ----------(b)(4)----------.

f. Accuracy was established across the range of the method using ----------(b)(4)---------concentration of the sample. As this method is described as an ----------(b)(4)----------, please provide an evaluation of accuracy by spiking the Drug Product with actual product-related impurities to levels that would bracket the b(4) specification.

g. You have determined that the linearity/range of the assay is –b(4)---------- which is equivalent to the 20-120 µg drug product doses prepared according to the method. Please clarify what the (b)(4)---------- is according to the SOP. Please provide data to show that –b(4)---------- is equivalent to 20-120 µg drug product.

h. Please provide data to support the lower limit of quantitation of the method.

27. The following comments relate to the Aluminum Determination of Drug Product (Sections 3.2.P.5.2 and 3.2.P.5.3).

a. Please provide a fully descriptive procedure.

b. In Section 3.2.P.5.2.3.1 (Standard Curve Preparation), it states that "Typically b(4) concentrations ranging from approximately –b(4)-- are prepared." Please specify the actual concentration range to be used in practice of the assay. Please revise your procedure to use b(4) concentration points.

c. In Section 3.2.P.5.2.3.3 (Sample Preparation), it states that samples are ----------(b)(4)----------. Please specify the time to which samples of the MnB rLP2086 Drug Product are to be ---(b)(4)--- what other criteria is used to determine the -------(b)(4)-------.

d. The Validation report summary for Aluminum (Section 2.5.11, Experimental Design) describes the evaluation of linearity based on ----------(b)(4)----------. Please submit an evaluation of linearity using at least (b)(4) concentrations levels to cover the intended range of the assay procedure..

28. The following comments relate to the Assay for ----------(b)(4)---------- of Drug Product (Sections 3.2.P.5.2 and 3.2.P.5.3).

a. The method as described does not include measurement and acceptance criteria for –b(4)---------- system suitability. –b(4)---------- ---------performance in terms of ----b(4)---------- well as ---b(4)---- ---------- should be part of acceptance criteria for the assay. Please incorporate these system suitability parameters into your method.

b. On page 23 of 25 of SOP-13655 we saw ----------(b)(4)---------- -------. Please provide the identity of this (b)(4). Please provide an approximate area percent of this (b)(4).

c. In the "Summary Report for the Validation of the Method for –b(4)---------- ---------- for MnB Bivalent rLP2086 Drug Product" (Section 2.3, Accuracy), it states that b(4) different concentrations were prepared and each concentration was analyzed b(4) times. The concentration was calculated and compared to the theoretical value." Please explain what the basis for the "theoretical value" is.

d. Batch Results for b(4) batches of 120 mcg Process Validation / Primary Stability Lots b(4) show –b(4)---------- ----------. Please explain the relationship between the observed higher recoveries relative to the Accuracy results ---b(4)---------- ----------

29. The following comments relate to the release and stability testing of drug product.

a. You propose to remove the ---(b)(4)--- pyrogenicity as a release test. We acknowledge that while pyrogenicity was not included as a release test in your pre-BLA meeting material, we did not discuss concerns about the removal of this test in the 1 May 2014 meeting. During review of the BLA, we have determined that we do not concur with removal of the pyrogenicity test as the MnB rLP2086 vaccine can induce some degree of pyrogenicity. Please add the ---(b)(4)--- pyrogenicity test as a release test.

b. You propose to remove the General Safety Test (GST) as a release test for drug product. You state that other tests are in place to guarantee the safety of the vaccine, such as the bacterial and fungal sterility. We do not concur with your proposal at this time. Please add the GST as a release test. You may submit a post approval supplement to request exemption from the GST once an adequate amount of lots have been manufactured and tested.

c. ----------

----------(b)(4)----------

----------(b)(4)----------

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30. You have provided the list of various lots on stability. In addition, you are required by the regulations to keep retention samples. Please confirm that none of the retention or stability samples have "Agglomeration" which is defined as "Liquids with Inhomogenous Suspension".

31. You have provided the Post Approval Stability Protocol and Stability Commitment in Table 3.2.P.8.2-1. You propose to perform the -------(b)(4)------- sterility at time zero and ---(b)(4)---. Please add ---(b)(4)--- testing time-points on an -(b)(4)- basis. In addition, you also state that testing will be performed at the currently approved end of shelf life. Please confirm that you will perform ----(b)(4)---- sterility testing at 24 months.

32. You state in Section 3.2.P.2.3.3 that "Based on the release, characterization, and stability data generated to date on -(b)(4)- lots and (b)(4) Pfizer lots, the DP manufactured at the (b)(4) sites are considered comparable." You have provided the release and stability data. Please provide the characterization data that you are referencing in this Section.

33. Please provide your definition of date of manufacture from which the expiry date is calculated.

34. You are requesting the following potential drug product exposure times and temperatures from the end of filling to market receipt.

- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------

You have provided 6 months of accelerated stability data –b(4)---------- process validation lots. You have also provided 12 months of -b(4)-- data on b(4) process validation lot (--b(4)---------- for the duration of the study). We note that the –b(4)---------

---- data does not mimic the storage conditions requested above. In addition, -b(4)- potency data was not included in the -----(b)(4)-------- study. Please provide data, including –b(4)- potency, to support the above exposure time and temperature request. Alternatively, please revise your shipping storage temperature to between –b(4)----------.

LRP: Please note that additional comments for the LRP may arise based on your response to this IR.

35. You have added the –b(4)---------- for Drug Substance Subfamily A and B. Please also add the –b(4)---------- for Filled Vaccine..

General:

36. Please confirm that no Comparability Protocols were submitted with this BLA to request a future change to be downgraded to an Annual Report. We note that you submitted a section for qualification of future reference material (Section 3.2.S.5). The information provided in this section does not include a detailed Comparability Protocol. A post approval supplement can be submitted to request a Comparability Protocol for downgrading future changes to Annual Report. Please confirm.

37. You committed to submit the results of other characterization studies, including data from ----------(b)(4)----------, to the BLA to address purity in our meeting on 1 May 2014. These characterization studies were not included in your submission. Please provide the results of the characterization studies, including data from ----------(b)(4)----------, to address purity of your ----------(b)(4)-- drug product.

38. In Section 3.2.S.2.2 entitled, Description of Manufacturing Process and Process Controls – Filling, Storage and Transportation, subsection 3.2.S.2.2.2 entitled, ------(b)(4)----- Storage you state that, "----------(b)(4)---------- Please submit information on the -------(b)(4)------; specifically, equipment description, equipment qualification and –(b)(4)-----validation.

In your reply to this information request, we recommend that you restate the item and follow it with your explanation or clarification. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference. If you have any questions, please contact CDR Mike Smith, Ph.D. at 301-796-2640.