Information Request Email, August 25, 2014 - GARDASIL 9

From: Khurana, Bharat
To: alison_fisher@merck.com
Cc: Montague, Laura
Subject: STN 125508/0 (Gardasil 9); Information Request #17
Date: Monday, August 25, 2014 10:32:00 AM

Dear Alison,

We have the following requests for information regarding your supplement 125508/0:

1. In follow-up to comment #2b from the Information Request of May 30, 2014, please provide a summary of the currently available results of the performance and functionality testing of the syringe used to supply the 9-valent HPV vaccine, including a description of any deviations that occurred during this testing.
2. In follow-up to comment #3 from the Information Request of May 30, 2014, and the telecon of July 10, 2014, regarding your developmental data and protocols,

   a . Please submit the results of the PQ studies to validate sterilization of Load Patterns ----------(b)(4)---------- in autoclaves ----------(b)(4)---------- when available.

   b. Please submit the results of the PQ studies to validate sterilization of Load Patterns ----------(b)(4)---------- in autoclaves ----------(b)(4)---------- when available.
3. In follow-up to comment #5b from the Information Request of May 30, 2014, we do not agree that the data you have provided supports that you have satisfactorily validated cleaning of your (b)(4) tanks due to the presence of white particles and process-related residue after cleaning. We have the following comments:

   a . Investigation report 2011-135-0038 states that there were 17 occurrences of particles found in a tank between September 2010 and September 2011. Please provide a list of the tanks in which these particles were observed. Please also clarify if such particles have been observed since the implementation of the CAPA as stated in the report, and describe these occurrences.

   b. Please provide a summary of the cleaning validation data for all effected tanks used in the 9-valent HPV manufacturing process which supports that the CAPA implemented to prevent the build-up of process-related residues and the observed white particles was successful. Such validation data should support that the process piping connections are maintained in a clean condition.
4. In follow-up to comment #5c from the Information Request of May 30, 2014, we do not agree that the presence of ----------(b)(4)---------- tanks, and potentially in your product, is acceptable. We have the following comments:

a . Please clarify is these -----(b)(4)----- have been observed in any tanks other than the --------(b)(4)--------- tanks described in final report TW #539800, and identify these tanks.

b. Please clarify if ------(b)(4)------ have been observed in any tanks used to manufacture the quadrivalent HPV vaccine, and identify these tanks.

c. We do not agree with your assessment that the ----------(b)(4)---------- or that your system prevents all of the ----(b)(4)----- from entering your product final containers. We also do not agree that the generation of these ----(b)(4)---- is an acceptable and an inherent part of your manufacturing process, as this generation process is potentially caused by equipment defects. Please develop and implement a CAPA that addresses resolution of the generation of ----------(b)(4)--- in all of the tanks for which such particles have been observed, and provide validation data that supports that this CAPA is effective.

5. In follow-up to comment #6 from the Information Request of May 30, 2014, please submit the results of annual revalidation of the ----------(b)(4)---------- when available, as described in the amendment of June 30, 2014.

6. In follow-up of comment #8b from the Information Request of May 30, 2014, we do not agree that the results of the invalid cleaning validation of the ----------(b)(4)---------- can be dismissed due to successful validation of cleaning of the other HPV Types. It appears that your established protocol to validate cleaning of this equipment requires a successful demonstration of your ability to clean ----(b)(4)---- from this equipment, since you conducted this study as part of your validation, and therefore providing a justification of why results from the study are not necessary is unacceptable. We again request that you submit the results of a study that confirms your ability to clean ----------(b)(4)----------.

7. In follow-up of comment #9 from the Information Request of May 30, 2014, we do not agree with your bridging of the cleaning after ----------(b)(4)----------. It appears that your established protocol to validate cleaning after ----------(b)(4)---------- included the requirement to validate cleaning after ----------(b)(4)----------, and you have not provided data validating cleaning for ----------(b)(4)----------. Please submit data that supports validation of cleaning of ----------(b)(4)----------.

8. The ----------(b)(4)---------- is well above the results obtained that are reported in your submission (range -----(b)(4)------). We have the following comments:

a . Please provide a justification for this specification.

b. Please clarify if there is an alert limit in place for this test to determine when there is a trend towards higher ---(b)(4)---.

c. Please clarify if you plan to adjust this specification to more closely meet process capabilities when you have collected more historical data.

9. Regarding the media fills conducted to simulate formulation, syringe filling and vial filling,

   a . Please clarify and describe if these media fills were conducted using worst-case conditions.

   b. Please clarify how the volume of media formulated or filled relates to the maximum volume and lot size of 9-valent HPV vaccine you plan to formulate and fill.

10. Regarding the ----------(b)(4)---------- Testing conducted for the ----------(b)(4)----------

    a. Please confirm if positive controls were used, and describe these positive controls in detail, including the manner in which they were created and their dimensions.

    b. Please confirm that the ----------(b)(4)---------- Testing are the actually ---(b)(4)--- planned for the 9-valent HPV vaccine (versus the ---(b)(4)--- currently used for the quadrivalent HPV vaccine).

11. Please clarify what equipment qualifications have been completed to support mixing of the 9- valent HPV vaccine product, and supply summary reports for these studies/qualifications.

Please submit your response as an amendment to STN 125508/0 at the earliest possible. If you prefer having a teleconference with CBER to discuss the above issues prior to responding, let us know. As always, please feel free to contact Laura Montague or myself if you have any questions.

Thanks,
Bharat

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