Information Request Email, May 30, 2014 - GARDASIL 9

RECORD OF EMAIL COMMUNICATION
Submission Type: BLA Submission ID: 125508/0 Office: OVRR
Product: Human Papillomavirus 9-valent Vaccine, Recombinant
Applicant: Merck Sharp & Dohme Corp.
Telecon Date/Time: 30-May-2014 12:20 PM
Initiated by FDA? Yes
Telephone Number: N/A (email)
Communication Category: Information Request
Author: Bharat Khurana
Telecon Summary: IR #11 – from DMPQ regarding equipment, syringes, autoclaves, environmental monitoring, and validation of tank cleaning
FDA Participants: Bharat Khurana
Non-FDA Participants: Alison Fisher
Trans-BLA Group: No
Related STNs: None
Related PMCs: None
Telecon Body:

From: Khurana, Bharat
Sent: Friday, May 30, 2014 12:20 PM
To: alison_fisher@merck.com
Subject: STN: 125508/0: Information Request #11
Dear Alison,
We have the following information requests regarding your supplement 125508:

1. Please provide a list of all ***new*** pieces of equipment that are used for the manufacture of the 9-valent HPV vaccine, including a brief description of each item, the building and room number where the each items is located, and the manufacturing step(s) that each item is used.
2. Regarding the syringe used to supply the 9-valent HPV vaccine:
   a. Please confirm that the syringe (barrel, stopper and rod) is the same as the syringe used for the licensed quadrivalent HPV vaccine.
   b. Please provide a summary of the syringe performance and functionality testing that has been completed.
3. We reference your email of May 9, 2014, containing a plan to address the performance qualifications for autoclave sterilization of equipment used during manufacturing of the 9-valent HPV vaccine in ----------(b)(4)------, and our acceptance of this plan during the telecon of May 14, 2014. In your planned submissions to address our concerns, please be sure to address the following items:

a. Regarding the performance qualification for sterilization of equipment used during manufacturing of the 9-valent HPV vaccine in autoclaves ----------(b)(4)---------- using ----------(b)(4)----------:

i. Please provide the results of preliminary performance qualification studies (i.e., studies that you have designated as developmental) that are scientifically sound and valid to support the identification of worse case equipment challenge items for further performance qualification studies. The protocols for these studies should include:

1. Run validity criteria consistent with the further performance qualification studies. (i.e., the number of allowed failed thermocouple probes).
2. Defined evaluation criteria for critical assessments. For example, if you choose to use “mock” biological indicators to evaluate potential interferences of ----------(b)(4)----------, you must have defined evaluation criteria and provide data supporting the acceptability of their use. Alternatively, actual biological indicators with a defined acceptance criterion of no growth can be used.
3. Consistent load configurations requirements. For example, if maximum load configurations are specified, then all runs (except for the evaluation of the minimum load) should be performed under the same conditions.

ii. Please provide the results of further performance qualification studies that support microbial lethality and reproducibility of your production load configurations. The following concerns should be addressed:

1. If the results of the preliminary performance qualification studies, conducted as described above, change the challenge items in the maximum and minimum loads as well as the identity of the worst case load selected in the performance qualification studies, then these studies should be repeated using the new challenge items and worst case loads.
2. Your protocol should have an evaluation criterion to verify that the chosen worst case load configuration for reproducibility studies was worst case as compared to the other load configuration types chosen for one run confirmatory studies.
3. Since you intend to use a production autoclave cycle with ----------(b)(4)----------, the following additional information should be provided:

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

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

iii. Please provide a production SOP which includes the following information:

1. Instructions for preparation of your final validated production load configurations.

2. ----------(b)(4)----------.
iv. Please provide the portion of the batch record for the most recently manufactured batch of the 9-valent HPV vaccine that describes the sterilization of equipment in autoclaves ----------(b)(4)---------- in ---(b)(4)--- using ----------(b)(4)----------, and includes the actual loads used, the actual cycle parameters used, and copies of the full cycle hardcopy autoclave run printouts, as well as a description of any differences between the load pattern/cycle used for this batch and the load pattern/cycle used for the performance qualification.
b. Regarding the performance qualification for sterilization of equipment used during manufacturing of the 9-valent HPV vaccine in autoclaves --------(b)(4)---------- in ----------(b)(4)----------:
i. Please provide the results of preliminary performance qualification studies (i.e., studies that you have designated as developmental) that are scientifically sound and valid to support the identification of worse case equipment challenge items for further performance qualification studies. The protocols for these studies should include:
1. Run validity criteria consistent with the further performance qualification studies. (i.e., the number of allowed failed thermocouple probes).
2. Defined evaluation criteria for critical assessments. For example, if you choose to use “mock” biological indicators to evaluate potential interferences of ----------(b)(4)----------, you must have defined evaluation criteria and provide data supporting the acceptability of their use. Alternatively, actual biological indicators with a defined acceptance criterion of no growth can be used.
3. Consistent load configurations requirements. For example, if maximum load configurations are specified, then all runs (except for the evaluation of the minimum load) should be performed under the same conditions.
ii. Please provide the results of further performance qualification studies that support microbial lethality and reproducibility of your production load configurations should be provided. The following concerns should be addressed:
1. If the results of the preliminary performance qualification studies, conducted as described above, change the challenge items in the maximum and minimum loads as well as the identity of the worst case load selected in the performance qualification studies, then these studies should be repeated using the new challenge items and worst case loads.

2. Your protocol should have an evaluation criterion to verify that the chosen worst case load configuration for reproducibility studies was worst case as compared to the other load configuration types chosen for one run confirmatory studies.
3. Since you intend to use a production autoclave cycle with ----------(b)(4)----------, the following additional information should be provided:

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

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

iii. Please provide a production SOP which includes the following information:
1. Instructions for preparation of your final validated production load configurations.
2. ----------(b)(4)----------.

iv. Please provide the portion of the batch record for the most recently manufactured batch of the 9-valent HPV vaccine that describes the sterilization of equipment in autoclaves ----------(b)(4)---------- in ----(b)(4)--- using ----------(b)(4)----------, and includes the actual loads used, the actual cycle parameters used, and copies of the full cycle hardcopy autoclave run printouts, as well as a description of any differences between the load pattern/cycle used for this batch and the load pattern/cycle used for the performance qualification.

4. Please provide the protocol and study report for the performance qualification of environmental monitoring in Formulation Suite (b)(4) in ---(b)(4)---.
5. Regarding the validation of the cleaning of ---(b)(4)--- tanks in ------(b)(4)------, please provide the following items:

a. Documentation that supports that these tanks are equivalent.

b. In follow-up to the observation of ----------(b)(4)----------, a copy of the Deviation Alert #135-2001-105 and Investigation #2001-135-0038.

c. In follow-up to the observation of ----------(b)(4)----------, a copy of Product Impact Assessment #57300-2001-TS-0217.

6. You indicate that ----------(b)(4)---------- located in ---(b)(4)--- are new pieces of equipment for the 9-valent HPV vaccine. Please provide the initial sterilization validation protocol and reports for these tanks.
7. You indicate that the ----------(b)(4)---------- was re-implemented after being out-of service since its installation in (b)(4) and that modifications were made to improve the (b)(4) decontamination. Please clarify if the re-implementation of the -------(b)(4)------- and modifications were reviewed by CBER under a previously submitted supplement (and provide the STN), or if this is a new decontamination method being implemented for the 9-valent HPV vaccine.
8. In the report for study 8-7020-B16, describing the initial cleaning validation for HPV Type 58 in ----------(b)(4)---------- you indicate that there was a ----------(b)(4)----------, and that this study was considered invalid. Please address the following comments:
   a. Please provide a copy of the investigation report (#200171754) and a description of what actions were taken (if any) to address the apparent equipment design flaw.
   b. Since this study was considered invalid, please provide the results of a valid study that confirms your ability to clean HPV Type 58 from this equipment.
9. For the validation of ----------(b)(4)----------, you state that the validation considered a total of --(b)(4)-- for all HPV Types. However, you state that for HPV Type 52 -----(b)(4)--- you only validated ----(b)(4)---- and that ------(b)(4)------ for HPV Types 33 and 58 were bridged to the validation for HPV Type 52. Please clarify the ----------(b)(4)---------- that is validated for HPV Type 33, 51 and 58 in ----------(b)(4)----------, and if you consider ----(b)(4)---- validated for these HPV Types, please provide a rationale.

Please submit your response as an amendment to STN 125508/0 and as always, please feel free to contact Laura Montague or myself if you have any questions.
Thanks,
Bharat

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