Information Request Email, June 27, 2014 - GARDASIL 9

From: Khurana, Bharat
To: alison_fisher@merck.com
Subject: STN 125508/0: Information Request #14
Date: Friday, June 27, 2014 3:57:00 PM
Dear Alison,
As we review STN 125508/0, we have the following CMC related Information requests:

1. The submission refers to ongoing stability studies for --------(b)(4)-------- drug product for the purpose of supporting proposed storage/expiry periods. Briefing information for a proposed meeting in July 2013 (IND13447/440; received 6/18/2013) mentions plans to submit updated stability data as they become available. Please provide an estimated date for providing updated stability data for --------(b)(4)-------- drug product. Please also include updated analyses, potential impact on specification modeling, and summary/conclusions if appropriate.
2. Regarding the reference standard for the (b)(4) assay, 3.2.P.6 (Reference Standards or Materials) describes ongoing stability data for working standard lot ----(b)(4)------. On p. 10, the following statement is found: *"Results demonstrate no statistically significant change in potency ((b)(4)) through the -(b)(4)- time point for HPV Types 6, 16, 18, 31, 45, 52, and 58. While HPV Types 11 and 33 were statistically significant,* ***only the assay positive control for HPV Type 11 was statistically significant****; however, the lower and upper 95% mean results are predicted to remain between* ***the established assay control limits for HPV Type 11*** *until at least September 2016".* Please clarify the following:
   - The meaning of the phrase, *"only the assay positive control for HPV Type 11 was statistically significant"*, is not clear. If this refers to a change in potency values over time for this positive control, what mechanism accounts for this trend ? The positive control is understood to be ----------(b)(4)---------- and therefore presumed to be stable indefinitely.
   - Please provide more details regarding “the established assay control limits for HPV Type 11” in this context. More generally, please provide the pre-specified criteria used to either reject or accept expiry extensions for potency reference standards on the basis of similar stability data.
3. The HPV clinical PCR assay descriptions are found in 5.3.5.1 Study Report Body P001. Please provide the validation summary and validation reports for these assays.

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

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