

To: Mr. Matt Whitman  
File: STN 125259/0 CERVARIX  
RE: Request for CMC information  
Date: August 7, 2007

**APPROVED**

*By Helen Sullivan Demignani at 4:15 pm, Mar 11, 2008*

We have the following comments regarding CMC information included in the BLA:

1. Please submit any additional data that may be available regarding characterization of the (b)(4) "cellular feature".

2. You state that commercial scale monovalent adsorbed bulk lots will range in volume from (b)(4). We have the following comments:

(a) Please discuss what factors determine the volume of the monovalent adsorbed bulk product in the manufacturing process (e.g., whether a bulk lot will be (b)(4)).

(b) Please clarify whether the manufacturing process has been validated for this volume range of bulk material.

3. We note that the commercial scale lots will range in size from (b)(4). We have the following comments:

(a) Please describe how you determined that the final container lots will be manufactured in this volume range.

(b) Please clarify whether the formulation process has been validated for this volume range.

4. You state that each final formulated bulk can be used to fill (b)(4) final container lots. We have the following comments:

(a) How will the volume for each final container lot be determined?

(b) How will the final bulk material be stored?

(c) How will the final bulk material be aliquoted when it is (b)(4) final container lots?

(d) Please discuss the quality control measures that are in place to ensure the sterility of the stored final bulk material.

5. Based on stability information included in the BLA, we note that you potentially could store adsorbed virus-like particles (VLPs) either as (b)(4) formulated bulk, or final container

product for up to (b)(4) (i.e., combined storage time at (b)(4)). We note that you have proposed a sequential, long-term stability study that will cover the maximum potential storage time of (b)(4) as a post marketing commitment.

Please provide information regarding the age of the monovalent bulk lots that were used for formulating each final container lot that is on stability study. Specifically, we request that you include the lot traces (i.e., specify the bulk lots that were used to formulate each final container lot on stability study), the date of manufacture of the final container lot, and the calculated age of the bulk at the time of fill.

. Please submit translations of the following monographs:

(a) Monographs #4412 and #4452 (Preparation of the HPV-16 inoculum and HPV-18 inoculum,

respectively)

(b) Monographs #4409 and 4410 (Production of HPV-16 and HPV-18 antigen purified bulks, respectively)

(c) Monographs #4413 and #4432 (Production of adsorbed monovalent bulks for HPV-16 and HPV-18, respectively)

(d) Monograph #3861 (Production of MPL (b)(4))

(e) Monograph #4434 (MPL adsorbed bulk production)