

To: Mr. Matt Whitman
File: STN 125259/0 CERVARIX
RE: Comments regarding assay validation
Date: September 7, 2007

APPROVED
By Helen Sullivan, Campaigner at 2:20 pm, Mar 11, 2008

We have the following comments regarding assessment of antigenic activity of the HPV-18 L1 VLP by (b)(4) (m3.2.S.4.3, Section 6):

1. Please clarify the definition of (b)(4) of the dose-response curve used in your assay validation (Section 6.1.2, Page 18). Additionally, please provide a detailed explanation and your justification of the acceptance criterion for (b)(4) of the dose-response curves.
2. You state that inter-dilution CV for all L1 VLP antigen content values range between (b)(4) (Section 6.2, Page 18). We note that in Table 10 (Page 18), the CV for theoretical starting concentration of (b)(4) is stated to be (b)(4) (column 3; 10/03/04). This value is outside the (b)(4) (b)(4) interval. Please comment.
3. Please justify using CV (b)(4) for determining whether the starting concentration is suitable in your analysis described in Section 6.2 (Page 18).
4. Regarding evaluation of the range, we have the following comments:
 - (a) We note that the ratio of calculated starting concentration/theoretical starting concentration (b)(4) from (b)(4) as the theoretical starting concentration (b)(4) from (b)(4) (data in last column of Table 10 on Page 18). These data show systematic deviation from a proportional relationship between the calculated and theoretical values in this range. However, you conclude that the data presented in Table 10 "demonstrate that there is a proportional relationship between the calculated and theoretical values for starting concentrations ranging from (b)(4)." Please comment.
 - (b) If you consider the deviation from proportionality to be acceptable, please provide your justification.
5. For analysis of reproducibility (Section 6.3.3, Page 20), please calculate the 95% confidence interval for the inter-laboratory difference.
6. Please clarify whether your assay validation included assessment of operator-to-operator and day-to-day variability. If these parameters related to your assessment of precision were evaluated, please provide the data. If these analyses were not performed, please explain why you do not consider assessment of these parameters to be relevant for this assay.

We have the following additional comment regarding your assessment of antigenic activity of the HPV-16 L1 VLP by (b)(4) (m3.2.S.4.3, Section 6):

7. For your analysis of reproducibility (Section 6.3.3, Page 18), please calculate the 95% confidence interval for the inter-laboratory differences.

In your reply to this memo, we recommend that you restate each item and follow it with your explanation or clarification. Please note that we may have additional comments regarding assay validation as we continue our review of the BLA.