

**APPROVED**

*By Helen Sullivan Gemignani at 2:29 pm, Mar 11, 2008*

To: Mr. Matthew Whitman

File: STN 125259/0 CERVARIX

RE: Developmental Toxicity Studies BRV 249 and 1729/8

Date: August 31, 2007

The following comments pertain to your developmental toxicity assessments:

It is not clear whether the finding of ventricular septal defect (IVSD) observed in pivotal study (b)(4) 249 and study 1729/8 ~ D6154 is a treatment related finding, since it is isolated in nature, i.e., occurrence in 1 fetus per litter/group and also observed in the historical control data. However, the incidence of ventricular septal defect in both the rabbit study conducted with MPL (study 1729/8-D6154), as well as in the pivotal study (study (b)(4) 249) conducted in rats with HPV/AS04D, appears higher than what was observed in the historical control. Furthermore, in the rabbit study treated with MPL, this finding occurred in the higher dose groups only. In the pivotal study (b)(4) 249, in which this event was observed (groups 3 and 4), animals received additional doses of the vaccine prior to mating compared to animals in group 2.

1) Please perform a statistical analysis of the data from pivotal study (b)(4) 249 and study 1729/8 to evaluate the statistical significance of the finding of IVSD. We acknowledge that this analysis would be post-hoc.

2) Please provide a reference supporting your statement that the finding of IVSD represents a delay in development and an explanation of your finding of the IVSD being "small" as used to describe the finding in study (b)(4) 249.