



Record of Telephone Conversation

<b>STN Number:</b>	125259/0
<b>Manufacturer:</b>	GlaxoSmithKline Biologicals
<b>Product:</b>	Human Papillomavirus Vaccine, ASO4 Adjuvant-Adsorbed

**To:** File  
**From:** Helen S. Gemignani, Regulatory Project Manager  
**Subject:** Discussion of Complete Response Letter Safety Items  
**Date:** January 16, 2008      **Time:** 09:00 – 10:20 am  
**Initiated by:** GSK  
**Contact:** Mr. Whitman 610 787-3726

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**Signature:**  
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**Summary of Telecon**

GSK submitted the following document to CBER in preparation for this telecon. The first column is a restatement of the items in CBER's December 14, 2007, Complete Response letter. The second column is GSK's proposal for response. Each item is followed by CBER/GSK discussion of that item.

**Responses to questions/requests identified in the Complete Response letter for Cervarix® - Safety**

<b>Item</b>	<b>Question/request cited in the CR letter of FDA</b>	<b>Proposal of GSK / Point(s) for Clarification</b>
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1. Your product contains both HPV Virus Like Particles Adsorbed and AS04 adjuvant, added to enhance the immune response to the HPV vaccine antigens. We have determined from our review that there are numerical imbalances for neuroinflammatory adverse events and potential autoimmune musculoskeletal events in the two treatment groups (vaccine vs. control), and potentially other adverse events. Given the imbalances observed in subjects who received Cervarix compared to those receiving controls, we are concerned about the possibility that these imbalances may be due to the adjuvant. Under 21 CFR 610.15(a), an adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety of the product. Please describe how you will address this requirement
- With respect to the adjuvant system AS04, GSK will address all the questions raised by CBER as well as augment the application with additional safety data and expert opinion. CBER will be provided with the advice of independent experts consulted by GSK regarding specific events of interest. Finally, available post-marketing surveillance information will be provided.

**Item 1 Discussion:** CBER stated that they will await the submitted response and review. CBER asked GSK to provide, in their response, the names of GSK's independent experts and what their evaluations and opinions are and which type of information they want to review. CBER asked whether GSK is looking into the imbalance of pregnancy outcomes. GSK is reviewing this internally and does not have external contacts as of yet. CBER asked if GSK will be doing additional studies, in terms of item 1, on the safety of the adjuvant system. GSK will not be doing new studies for licensure.



2. At the time of the pre-BLA meeting, CBER raised the issue of presentation of blinded safety data, and stated that the Agency needed to ensure that adverse events could be readily identified and easily reviewable in the BLA (CBER minutes from pre-BLA meeting, May 1, 2006). GSK assured that all adverse events would be displayed by treatment group and by preferred term, and that the FDA could request any adverse event (AE) data not listed through the firewall group (GSK minutes of pre-BLA meeting, May 1, 2006; IND -(b)(4)-, Amendment 247, Serial 248). However, we are unable to complete our assessment of the safety of Cervarix because the data were presented incompletely in a blinded manner.

Additionally, regarding the deaths reported in the BLA, we note the following:

**Item 2 Discussion: CBER informed GSK that present medical cases of interest will be included in the VRBPAC briefing document and presented publicly at VRBPAC, in full, including disclosure of treatment received.**

- In summary of safety data section of the BLA (Module 2.7.4 Summary of Clinical Safety) five deaths in Study HPV-008 were reported up to the data lock point of September 30, 2006 (p. 103).

GSK understands that the procedures put in place for review of the BLA and subsequent responses to questions was not perceived as optimal by CBER reviewers and GSK would like to collaborate with CBER to ensure that an appropriate process will be implemented to facilitate CBER's review of the responses.

To this purpose, GSK is reviewing the current process in place for provision of unblinded data via a Firewall to CBER and is preparing a revised process for future discussion and agreement with CBER. As previously, this revised process will ensure all data provided to CBER is fully unblinded but in such a manner that the integrity of blinded ongoing studies is not impacted.

Acknowledged.



- Two additional deaths were reported to IND -(b)(4)- (one in study HPV-008 and one death in study HPV-009) which were possibly related to HPV 16/18 vaccine. We note that only one of these deaths (Subject \_\_\_\_ ) was included in the section discussion deaths in ongoing trials (Module 2.7.4 Summary of Clinical safety, section 2.1.2.2., pp.104-105.) Details regarding the other subjects in study HPV-008 (Subject \_\_\_\_ ) were included in the section of serious Adverse Events (SAEs) considered to be related or possibly related to vaccination (Module 2.7.4 Summary of Clinical Safety, Section 2.1.3.5, p.132), but the information provided did not include the fact that this subject had died. We acknowledge that this death occurred in February 2007, which was after the data lock point. However, this was still >1 month prior to the submission of the BLA and included in the total deaths that occurred in Cervarix studies.
- We note that several other deaths were included in the section on deaths in ongoing studies (Study HPV-009) Module 2.7.4 Summary of Clinical Safety, section 2.1.2.2., p. 103) and treatment allocation information was provided for four of five of these reported deaths upon request.
- We also note that in a recent presentation at the ACIP meeting (October 25, 2007), the five deaths noted within the Summary of Clinical Safety for Study HPV-008 (Module 2.7.4 Summary of Clinical Safety, Section 2.1.2.1.0, pp. 102-103) were the only ones included.

GSK acknowledges that one of the possibly related deaths occurred between the data lock-point (DLP) used for BLA and the actual submission of BLA. GSK will provide a summary of the overall history of reporting of this case and an explanation for why it was not included in the BLA submission.

Note that it is GSK's intention to provide CBER, upon request and prior to the VRBPAC meeting, an update of reported deaths from the DLP used for BLA.

Acknowledged.

Acknowledged. GSK will clarify why the ACIP presentation did not include a comprehensive overview of deaths reported in the HPV clinical program but only included a subset of deaths, i.e., the five deaths referenced in the comment. Of note, the ACIP presentation was intentionally limited to a summary of the deaths in the pooled safety analysis through a DLP of September 30, 2006.



**Item 2 Discussion: CBER stated that given the ACIP presentation, the public perception is that there are no safety concerns. Full disclosure will be necessary.**

- 2.a. In view of the information noted above, we request that you provide an updated presentation of the deaths that have occurred in clinical studies of Cervarix, including Study HPV-009. We request that you provide information regarding all deaths regardless of attribution (i.e., even if the death was not considered to be vaccine-related by the investigator). We request that you provide one comprehensive table listing all deaths as of September 30, 2007 and include information regarding treatment allocation, time to event relative to vaccination, and investigator attribution in each case.

With the intention of providing CBER with as complete an overview as possible concerning reported deaths, GSK proposes to provide an updated presentation of all deaths, regardless of attribution, for all clinical studies in which Cervarix has been administered, with a **DLP of December 31, 2007**. Thus and in addition to BLA studies, studies not included within the BLA will be considered, i.e., studies that started since the September 30, 2006 DLP used for the BLA and studies from GSK's other HPV programs.

A shell table of the information to be presented for each death is provided in Appendix Table 1. The data provided to CBER will be fully unblinded for all deaths and will be provided via a Firewall to ensure the integrity of ongoing studies.

In addition, the International Events Reports (i.e., CIOMS) for all deaths will be provided in annex to the complete response.

Upon request and prior to the VRBPAC meeting, GSK can provide an update of reported deaths as well as serious adverse events (SAEs) reported as possibly related to vaccination by investigators.

GSK point for clarification: Does CBER concur with this proposal? Does CBER anticipate the need for further safety updates (e.g. deaths) in advance of the VRBPAC?



**Item 2.a. Discussion: CBER stated that the proposed 12/31/07 Data Lock Point for deaths is acceptable. CBER requested that all deaths be updated at 2 months prior to VRBPAC. If additional cases are added to the table at that time, these should be highlighted and easily identifiable. International Safety Reports need to be submitted with any additional deaths.**



- 2.b. We note that Serious Adverse Events (SAEs) reported as possibly related to vaccination by investigators up to the data lock point of September 30, 2006, are presented in Table 42 of the Summary of Clinical Safety. This list is difficult to read and although most events have been unblinded, there are several that remain blinded. We request that you provide an updated table of such events through September 30, 2007. The information should be presented by diagnosis, treatment allocation, time to event, and outcome. Diagnoses should be grouped by System Organ Classes (SOC) group. Please use the table below as a guide on how to present adverse event data. [table redacted for brevity]

With the intention of providing CBER with as complete an overview as possible concerning SAEs reported as possibly related to vaccination by investigators, GSK proposes to provide an updated presentation of all such SAEs, for all clinical studies in which Cervarix has been administered, up to a **DLP of September 30, 2007**. Thus and in addition to BLA studies, studies not included within the BLA will be considered, i.e., studies that started since the September 30, 2006 DLP used for the BLA and studies from GSK's other HPV programs.

A shell table of the information to be presented for each SAE reported as possibly related to vaccination by the investigator is provided in Appendix Table 2. The data provided to CBER will be fully unblinded for all SAEs reported as possibly related to vaccination by the investigator and will be provided via a Firewall to ensure the integrity of ongoing studies.

The International Events Reports (i.e., CIOMS) for all SAEs reported as possibly related to vaccination by the investigator will be provided in annex to the complete response.

Upon request and prior to the VRBPAC meeting, GSK can provide an update of reported deaths as well as serious adverse events (SAEs) reported as possibly related to vaccination by investigators.

GSK point for clarification: Does CBER concur with this proposal?



**Item 2.b. Discussion: CBER requested that ALL SAEs regardless of investigator attribution be reported in tables with accompanying International Event Reports. GSK was asked to add a column to Appendix Table 2 indicating investigator attribution. These SAEs will need to be updated 2 months prior to VRBPAC. If additional cases are added to the table at that time, these should be highlighted and easily identifiable. International Event Reports need to be submitted with any additional deaths. Since an update will be required prior to VRBPAC, CBER requested that the data lock point be changed to 12/31/07 for the CR response. SAEs should be presented by system organ class, by treatment group and by study and treatment plainly identified.**

**CBER requested a confirmation that all safety reports submitted to IND -(b)(4)- will be presented in the table of SAEs by system organ class, treatment group and study. If not, CBER requested that this list be submitted with the CR response.**





- 2.c. Please provide an updated table of pregnancy outcomes through September 30, 2007, including information from studies 001/007, 008, 009, 012, 013, 014, 015, 016. Specifically, we have the following comments and requests:

GSK proposes to provide an update of the pooled safety analysis of pregnancy outcomes given in the BLA, **with a DLP of September 30, 2007**. Thus, this updated analysis will consider the studies requested by CBER, including HPV-009, as well as studies HPV-003, 004 and 005, and the extension of studies HPV-012, 013 and 014.

List of clinical studies to be included in analysis: Studies HPV-001, 003, 004, 005, 007, 008, 012, 013, 013 Ext, 014, 014 Ext, 015 and 016.

Two tables of results will be presented: overall pregnancy outcomes and pregnancy outcomes reported around vaccination (pregnancy in subjects for which last menstrual period occurred between 30 days before and 45 days after vaccination), as described in shell tables provided in Appendix Table 3 and Appendix Table 4. The data provided to CBER will be fully unblinded for all pregnancy outcomes and will be provided via a Firewall to ensure the integrity of ongoing studies.

GSK point of Clarification: Does CBER agree with the list of clinical studies to be included in the updated pooled safety analysis of pregnancy outcomes?

**Item 2.c. Discussion: CBER requested that pregnancy outcomes be provided through a data lock point of 12/31/07 with update at 2 months prior to VRBPAC. The studies listed in the second item (to include study HPV-009) are acceptable. Any new cases should be easily identifiable and International Event Reports submitted with the updated tables.**



2.c.i. The reported rates of spontaneous abortion are higher in the HPV vaccine group as compared to the HAV (control) group in Study HPV-008. You claim that the rates in both groups are lower than those reported in US epidemiological studies of spontaneous fetal losses from recognized pregnancies (13-16%). It should be noted that "fetal loss" includes live births, stillbirths, spontaneous abortions (including hydatidiform mole), and ectopic pregnancies. As shown in one of the publications which you cited (Goldhaber, 1991), "Omitting ectopic pregnancies decreased the estimate (rate of spontaneous abortions) to 11.9%." Therefore, the reported rates of spontaneous abortion may in fact be similar or even higher than those in US epidemiological studies. Please comment.

Acknowledged. GSK will address the rates for spontaneous abortions as reported in the available literature, compared to those reported in its clinical program with Cervarix, in light of CBER's comment.



- 2.c.ii. If the outcome was a spontaneous abortion, information regarding estimated time to conception (either prior to or after vaccination), attribution, treatment group and description of event should be included.

Listings of the requested information for spontaneous abortions will be provided as described in Appendix Table 5. The International Events Reports (i.e., CIOMS) for all spontaneous abortion outcomes will be provided in annex to the complete response.

Information collected in pregnancy cases only focuses on the date of the last menstruation period (LMP) and not the estimated date of conception, as the latter is less reliable. The date of conception is usually not known and ovulation varies in timings from onset of menstruation among different women and from cycle to cycle. However, the estimated date of conception will be calculated as the LMP + 14 days. This is based on the assumption that ovulation/conception occurs on cycle day 14 in the average 28 day menstrual cycle.

**Item 2.c.ii. Discussion: CBER stated that spontaneous abortions should be presented through a DLP of 12/31/07, with updates at 2 months prior to VRBPAC. GSK should include both LMP and estimated date of conception. Any new cases should be easily identified and be accompanied by International Event Reports.**

- 2.c.iii. Since an imbalance in the proportion of subjects with a spontaneous abortion from -30 to +45 days was noted for all studies included in the pooled safety dataset, we request that data from Study HPV-009 also be included in the updated table of pregnancy outcomes. We suggest that you use unblinded Tables 58 (p.178) and 60 (p.176) within Module 2.7.4, Summary of Clinical Safety, as guides for how the data in the updated table should be presented.

Acknowledged. In accordance with CBER's request, updated data on pregnancy outcomes will include data from Study HPV-009, as described in the proposed responses to questions 2c, 2c ii, 2c iv and 2d i.



2.c.iv. Given the imbalance in the number of stillbirths noted for the pooled data, we request that you include the number of stillbirths that occurred within Study HPV-009. We note that two stillbirths were reported in a blinded table from Study HPV-009. For each reported stillbirth, please provide information on the treatment group, time from vaccination to estimated date of conception, and time to event.

Listings of the requested information for stillbirths will be provided as described in Appendix Table 6. The International Events Reports (i.e., CIOMS) for all stillbirth outcomes will be provided in annex to the complete response.

	<b>Item 2.c.iv. Discussion: CBER requested reporting of stillbirths through 12/31/07, with update at 2 months prior to VRBPAC. Any new cases should be easily identified and be accompanied by International Event Reports.</b>	
2.d	Regarding pregnancies with abnormal infant outcomes, we note the following:	Acknowledged. GSK will comment on these observations.
	<ul style="list-style-type: none"> <li>There was a neonate with a ventricular septal defect (VSD) whose mother participated in Study HPV-009 and received _____. We acknowledge that a second neonate _____ also developed a ventricular septal defect, but the time interval between vaccination and estimated date of conception was _____.</li> </ul>	
	<ul style="list-style-type: none"> <li>Increased rates of similar defects were reported in animal developmental toxicology reports for MPL.</li> </ul>	
	<ul style="list-style-type: none"> <li>Two other neonates _____ were not included in the unblinded version of Table 59. One neonate _____ had _____ and the second neonate _____. Other congenital defects were identified in the review _____, but were not included in the summary table.</li> </ul>	
	<ul style="list-style-type: none"> <li>In total, 35 congenital anomalies were noted in the blinded table for pregnancy outcomes for Study HPV-009.</li> </ul>	



2.d.i.	<p>We request that you provide an updated presentation of pregnancies with abnormal infant outcomes through September 30, 2007. This table should include infants born to mothers participating in study HPV-009. The study in which the abnormality was noted should be specified. Information regarding treatment allocation and events should be prepared by an unblinded statistician and submitted to CBER for review. Additionally, we request that you submit any International Event Reports for such congenital anomalies. We recommend that you use the table provided below as a guide. [table redacted for brevity]</p>	<p>The definition for abnormal infant outcomes used by GSK for safety reporting includes congenital anomalies as well as other medically significant outcomes. To simplify the presentation of pregnancies with abnormal infant outcomes, GSK proposes to present in separate tables congenital anomalies and other medically significant outcomes (i.e., abnormal infant outcomes other than congenital anomalies). Congenital anomalies will be provided for all clinical studies in which Cervarix has been administered, up to a <b>DLP of September 30, 2007</b>. Thus and in addition to BLA studies, studies not included within the BLA will be considered, i.e., studies that started since the September 30, 2006 DLP used for the BLA and studies from GSK are other HPV programs (see shell in Appendix Table 7).</p> <p>Because the definition of abnormal infant outcomes other than congenital anomalies differs for all GSK studies and for the study managed by National Cancer Institute (NCI), HPV-009, these anomalies will be presented in one table for GSK studies included in the updated pooled safety analysis of pregnancy outcomes (DLP September 30, 2007), i.e., Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 (see shell in Appendix Table 8) and in another table for HPV-009 (DLP September 30, 2007) (see shell Appendix Table 9).</p> <p>The International Events Reports (i.e., CIOMS) for all abnormal infant outcomes will be provided in annex to the complete response.</p>
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	<b>Item 2.d. Discussion: CBER requested presentation of abnormal infant outcomes and congenital anomalies through 12/31/07, with update at 2 months prior to VRBPAC. Any new cases should be easily identified and be accompanied by International Event Reports.</b>	
2.e.	<p>Please provide a list of discontinuations from study participation due to adverse events for all Phase 2b and Phase 3 studies (controlled and uncontrolled) which were submitted in support of licensure. We request that you provide this information in one table and include study number, PID number, event, time from vaccination to event, severity, attribution of event, and outcome. We recommend that these events be arranged by System Organ Classes (SOC) category. If data are available from Study HPV-009, we request that you include this information in the table also.</p>	<p>GSK proposes to provide an updated presentation of study discontinuations due to all adverse events for all studies in the pooled safety analysis of the BLA, up to the DLP of September 30, 2007. Thus, this updated presentation will consider the studies requested by CBER, as well as Studies HPV-003, 004 and 005, and the extension of studies HPV-012, 013 and 014. The inclusion of Study HPV-009 within this presentation is still under examination and GSK is in consultation with NCI on this point.</p> <p>The data will be presented in a single unblinded table, as described in shell in Appendix Table 10.</p> <p>GSK point for clarification: Does CBER agree that GSK provides an updated presentation with a DLP of September 30, 2007?</p>
	<b>Item 2.e. Discussion: CBER requested study discontinuations due to AEs through 12/31/07, with updates 2 months prior to VRBPAC. Any new cases should be easily identified and be accompanied by International Event Reports.</b>	
2.f.	<p>Our review has identified neuroinflammatory events which were reported in clinical studies of GSK products and these are presented in Table A. In addition, another sponsor has shared with you information on a case of transverse myelitis in a Phase 3 trial involving an MPL-adjuvanted --(b)(4)--- product. We have the following items:</p>	<p>Acknowledged.</p>



2.f.i.	Please clarify whether all cases of neuroinflammatory events to date for GSK's MPL containing products (from both IND and non-IND studies) have been reported to CBER. If there are cases of neuroinflammatory events which have not been reported to CBER (e.g., cases which may have occurred more recently), we request that you submit this information to the Cervarix BLA and to the respective INDs.	GSK will provide a description of any new cases of neuro-inflammatory events detected after the DLP used for the MPL meta-analysis and up to a DLP of <b>September 30, 2007</b> .
	<b>Item 2.f.i. Discussion: CBER requested neuroinflammatory cases to be presented through 12/31/07 with update 2 months prior to VRBPAC. Any new cases should be easily identified and be accompanied by International Event Reports.</b>	



2.f.ii.	<p>Please provide an overall assessment (rather than a case-by-case diagnostic interpretation) of neuroinflammatory events which occurred in clinical studies with GSK's MPL –containing products, including those presented in Table A. We also request that you provide a similar assessment of the musculoskeletal events listed in Table B below (includes Study HPV-009). These overall assessments should include the estimated background rates with which these events occur. [Tables A and B redacted for brevity]</p>	<p>GSK will provide an overall assessment made by GSK in consultation with external experts of ALL neuro-inflammatory cases through the updated DLP of September 30, 2007, including cases listed in Table A as per Complete Response letter. For the updated assessment, estimated background rates will be provided where feasible.</p> <p>GSK intends to provide an overall assessment made by GSK in consultation with external experts of musculoskeletal events as described in Table B as per the Complete Response letter. For this assessment, estimated background rates will be provided where feasible.</p> <p>GSK point of clarification: GSK understands that the requested assessment of musculoskeletal events is limited to the events detailed in Table B. GSK seeks clarification on the methodology (criteria, terms) used for selection of subjects detailed in Table B (i.e. to better understand the basis for the ‘**’ footnote).</p>
	<p><b>Item 2.f.ii. Discussion:</b> CBER noted that the cases listed in Table B were located in the “wunsol” datasets. Cases were searched by system organ class = musculoskeletal and connective tissue disorders by treatment group in each study, with further searches for HLT NAME = Arthropathies NEC and Rheumatoid arthropathies. In addition, when reviewing the AEs in this system organ class, if there was an AE DESC of interest (e.g., Joint pains and stiffness of all joints as noted for subject PID 4593 in study 015), further details were requested. CBER requested an update of such events through 12/31/07, with another update 2 months prior to VRBPAC. Any new cases should be easily identified and be accompanied by International Event Reports.</p>	





2.g.	Please note that we are awaiting responses to requests for source documents available for subjects indicated to have experienced neuroinflammatory events and potentially autoimmune events in your Level 3 and Level 4 analyses (discussed during a teleconference between CBER and GSK on November 13, 2007). Please submit the source documents as soon as possible.	Acknowledged. Source documents for these subjects will also be provided to CBER when available.
2.h.	Please indicate if the case of multiple sclerosis reported in study HPV-010 has been reported to VAERS.	GSK will clarify whether or not this case was submitted to VAERS.
2.i.	We request that unblinded versions of all blinded safety tables be submitted to the BLA. Please respond.	<p>Acknowledged. As requested by CBER, all tables provided in the answer to Question 2 will be provided unblinded to treatment allocation.</p> <p>GSK point of clarification: Does CBER agree that the provision of unblinded versions of all blinded safety tables refers to the Complete Response? To ensure that GSK prepares an appropriate and revised process for providing completely unblinded data for CBER review, GSK invites CBER to discuss the issues they encountered in their review of the BLA with respect to blinding of data.</p>



	<p><b>Item 2.i. Discussion:</b> CBER stated that there was difficulty in reviewing the tables of adverse events because of the number of AEs that remained blinded within a great number of tables. There were many tables that were blinded within the clinical study reports and pooled safety data reports. The “wunsol” datasets were reviewed by system organ class by study and by treatment group to make sure there were no AEs that were missed in the tables. Multiple requests for narratives were required because as the datasets were searched, AEs of interest were identified, and further information was needed to assess the events. In the discussions at the pre-BLA meeting, the scope of the blinded events was underestimated. In retrospect, the DLP of 9/30/06 for the safety database was too far removed from the date of the BLA submission. Safety reports were received to the IND and were not represented in the tables of AEs, and there was concern that not all AEs were adequately presented and full disclosure was lacking. CBER has a responsibility to license a product that is both safe and effective. We cannot do this with such a large proportion of the safety data still blinded. As noted in the CR letter (2i), CBER requests that blinded safety tables (including supplemental safety tables and appendix safety tables) in the following clinical study reports be submitted in an unblinded manner: Study 008, 001, 001-Annex 1, 007, 007-Annex 1, 007-M24, 015, Pooled safety [Section 5.3.5.3], and in the Summary of Clinical Safety. There is an additional 1 + years of data since the original submission, and a DLP of at least 9/30/07 (and ideally for 12/31/07) for unsolicited AEs is warranted. All SAEs in each study report should be presented in an unblinded manner within each study, and case narratives linked clearly to the treatment group.</p>		
3.	<table border="1"> <tr> <td data-bbox="316 1249 885 1732"> <p>Regarding the meta-analysis of results for MPL-containing products, results of the statistical test for homogeneity of the common relative risks of Grave's disease tend to be statistically significant in both Level 2 and Level 3 analyses. This evidence of lack of homogeneity of relative risks across studies suggests that the overall summary analysis results may be subject to bias. Thus, further careful review of the data for each individual study regarding the rates of Grave's disease may be warranted. Please comment.</p> </td><td data-bbox="885 1249 1380 1732"> <p>GSK will comment on the homogeneity testing regarding Grave's disease including a review of data for each individual study, and will provide an assessment of this disease for the program.</p> </td></tr> </table>	<p>Regarding the meta-analysis of results for MPL-containing products, results of the statistical test for homogeneity of the common relative risks of Grave's disease tend to be statistically significant in both Level 2 and Level 3 analyses. This evidence of lack of homogeneity of relative risks across studies suggests that the overall summary analysis results may be subject to bias. Thus, further careful review of the data for each individual study regarding the rates of Grave's disease may be warranted. Please comment.</p>	<p>GSK will comment on the homogeneity testing regarding Grave's disease including a review of data for each individual study, and will provide an assessment of this disease for the program.</p>
<p>Regarding the meta-analysis of results for MPL-containing products, results of the statistical test for homogeneity of the common relative risks of Grave's disease tend to be statistically significant in both Level 2 and Level 3 analyses. This evidence of lack of homogeneity of relative risks across studies suggests that the overall summary analysis results may be subject to bias. Thus, further careful review of the data for each individual study regarding the rates of Grave's disease may be warranted. Please comment.</p>	<p>GSK will comment on the homogeneity testing regarding Grave's disease including a review of data for each individual study, and will provide an assessment of this disease for the program.</p>		

Additional questions/comments:

A 12 year old subjects who Menactra and Cervarix together and developed severe Stevens Johnson syndrome and required admission and treatment in the University of Chicago burn unit. The outcome is listed as unknown because the subject's father refused to allow the attending physician in the burn unit to provide follow-up information



regarding her progress and all test results. Do you have any additional information regarding this subject? [INTERNAL COMMENT: Such a severe event has NOT been reported for Menactra alone in the pre-licensure database nor in VAERS reports in the post-marketing period.]

This document focuses on safety. One of the comments provided to your company involved the lack of demonstration of statistically significant efficacy in the prevention of HPV 18 related CIN 2+ (although with a positive trend). Given the safety concerns raised, and the need to submit updated safety reports, have you considered postponing submission of CR responses until further efficacy data has accrued which may be more likely to demonstrate statistically significant differences in prevention of CIN 2+ related to HPV 18 for vaccine recipients as compared to active control recipients?

**Appendix Table 1 Overview of deaths reported for all clinical studies that include vaccination with Cervarix (OCEANS output, data lock-point of December 31, 2007)**

Study	Subject no.	Case ID	Event Preferred Term (System organ class)	Age	Gender	Treatment allocation	Investigator's causality assessment	Vaccine Dose

**Appendix Table 2 Serious adverse events reported by the investigator as possibly related to vaccination for all clinical studies that include vaccination with Cervarix (OCEANS output, data lock-point of September 30, 2007)**

Primary System Organ Class (code)	Primary Preferred Term (code)	Subject no. (Country)	Study No	Case ID	Age	Gender	Vaccine Dose no.	T (s)
Serious Adverse Events reported after vaccination with Cervarix								
Serious Adverse Events reported after vaccination with the control (description of control)								



**Appendix Table 3 Pregnancy outcomes overall for Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 (Total vaccinated cohort, data lock-point of September 30, 2007)**

Outcomes	HPV N =		ALU N =		HAV360 N =		HAV720 N =		Total N =	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Pregnancy ongoing										
Normal Infant										
Premature birth										
Abnormal infant										
Elective termination										
Therapeutic abortion										
Ectopic pregnancies										
Spontaneous abortion										
Still birth										
Lost to follow-up										
Not applicable										

HPV = HPV-16/18 vaccine group (Studies HPV-001, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016)

ALU = Al(OH)<sub>3</sub> control group (Studies HPV-001, 007, HPV-015)

HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)

HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)

N = number of pregnancies

n = number of pregnancies in a given category

Value = value of the considered parameter

% = n / Number of subjects with available results x 100

Notes

Twin pregnancies counted as one pregnancy

Spontaneous abortion includes missed abortion

Not applicable: e.g. mole, trophoblastic tumor

**Appendix Table 4 Pregnancy outcomes around vaccination for Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 (Total vaccinated cohort, data lock-point of September 30, 2007)**

Outcomes	HPV N =		ALU N =		HAV360 N =		HAV720 N =		Total N =	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%



Outcomes	HPV N =		ALU N =		HAV360 N =		HAV720 N =		Total N =	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Pregnancy ongoing										
Normal Infant										
Premature birth										
Abnormal infant										
Elective termination										
Therapeutic abortion										
Ectopic pregnancies										
Spontaneous abortion										
Still birth										
Lost to follow-up										
Not applicable										

HPV = HPV-16/18 vaccine group (Studies HPV-001, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016)

ALU = Al(OH)<sub>3</sub> control group (Studies HPV-001, 007, HPV-015)

HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)

HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)

N = number of pregnancies

n = number of pregnancies in a given category

Value = value of the considered parameter

% = n / Number of subjects with available results x 100

**Notes**

Pregnancies around-vaccination: pregnancy in subjects for which last menstrual period occurred between 30 days before and 45 days after vaccination (Subjects with missing date for last menstrual period are not included)

Twin pregnancies counted as one pregnancy

Spontaneous abortion includes missed abortion

Not applicable: e.g. mole, trophoblastic tumor

**Appendix Table 5 Description of spontaneous abortions for Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 (Total vaccinated cohort, data lock-point of September 30, 2007)**

Study	Subject no.	Age	Treatment allocation	Relationship	Gestationa l age	Date of LMP	Estimated date of conception	Time from last vaccination to EDC	Time from EDC to next vaccination

LMP: last menstruation period

EDC: estimated date of conception



**Appendix Table 6 Description of stillbirths for Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 (Total vaccinated cohort, data lock-point of September 30, 2007)**

Study	Subject no.	Age	Treatment allocation	Relationship	Date of LMP	Estimated date of conception	Time from last vaccination to EDC	Time from EDC to next vaccination	Time from vaccination to event

LMP: last menstruation period

EDC: estimated date of conception

**Appendix Table 7 Description of congenital anomalies in infants in all clinical studies in which Cervarix has been administered (Total vaccinated cohort, data lock-point of September 30, 2007)**

Treatment	Study	Mother's Case ID (Mother's subject no.)	Infant's Case ID	Infant's gender	Infant's age	Parent/Child Indicator	Preferred term	Time from last vaccination to estimated date of conception	Time from last vaccination to diagnosis

**Appendix Table 8 Description of abnormal infant outcomes other than congenital anomalies in infants in Studies HPV-001, 003, 004, 005, 007, 008, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 (Total vaccinated cohort, data lock-point of September 30, 2007)**

Treatment	Study	Mother's Case ID (Mother's subject no.)	Infant's Case ID	Infant's gender	Infant's age	Parent/Child Indicator	Preferred term	Time from last vaccination to estimated date of conception	Time from last vaccination to diagnosis



**Appendix Table 9 Description of abnormal infant outcomes other than congenital anomalies in infants in Study HPV-009 (Total vaccinated cohort, data lock-point of September 30, 2007)**

Treatment	Study	Mother's Case ID (Mother's subject no.)	Infant's Case ID	Infant's gender	Infant's age	Parent/Child Indicator	Preferred term	Time from last vaccination to estimated date of conception	Time from last vaccination to diagnosis

**Appendix Table 10 Study discontinuations due to adverse events for studies included in BLA (Studies HPV-001, 003, 004, 005, 007, 008, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016) classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort, data lock-point of September 30, 2007)**

Primary System Organ Class (code)	Primary Preferred Term (code)	Treatment allocation	Study	Subject no.	Severity	Relationship	Time to event (relative to vaccination)	Outcome

Inclusion or exclusion of Study HPV-009 to be confirmed.

CBER asked GSK when they intend to submit their complete response to the December 14, 2007, CR letter. GSK replied that they intend to submit the responses by piecemeal starting in February 2007 with the last piece submitted by the end of the first quarter, March, 2007.

**End of Teleconference**



### **Action Items**

- GSK will implement a better working firewall for the duration of the Cervarix review.
- GSK will submit a table with a snapshot of their clinical trials database.
- Dr. Miller will demonstrate to GSK how she captures adverse event within the eBLA to help GSK understand how she is accessing information.

### **FDA Participants**

- Nancy Miller
- Rose Tiernan
- Martha Lee
- Robin Levis
- Helen Gemignani
- Douglas Pratt
- Lewis Schrager
- Florence Houn

### **GSK Participants**

- Dominique Descamps, MD - Clinical
- Gary Dubin, MD - Clinical
- Barbara Howe, MD - Clinical and Regulatory
- Clare Kahn, PhD – Regulatory
- Nicholas Perombelon, PhD – Clinical
- Anne Schuind, MD – Clinical
- Sharon Shapowal, RPh – Regulatory
- Fernanda Tavares, MD - Clinical safety
- Tom Verstraeten, MD - Clinical safety
- Martine Wettendorff, PhD - R&D
- Matt Whitman - Regulatory
- Toufik Zahaf, PhD – Statistician