Cervarix

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
WS/2365	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is	26/04/2023		SmPC, Annex II, Labelling and PL	The SmPC Section 4.4 (Bexsero), 6.5 and 6.6 has been updated as follows: Deletion of statement concerning the presence of natural rubber, revision of details for prefilled syringe. Editorial amendments have also been included.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	an integrated part of the primary packaging				Annex II of the Product Information of Twinrix Adult, Twinrix Paediatric and Ambirix in order to list GlaxoSmithKline Biologicals s.a., Parc de la Noir Epine, Avenue Fleming 20, 1300 Wavre, Belgium. The Patient Leaflet has been updated accordingly.
IB/0121	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	27/03/2023	n/a		
II/0117	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/03/2023	n/a		
II/0115	Submission of the final report from study HPV-027 listed as a category 3 study in the RMP to fulfil MEA/024.2; this is a long-term follow-up registry-based cohort study of HPV vaccine effectiveness against cervical pre-cancerous lesions and cervical cancer in a cohort of females previously enrolled from Finland in study HPV-008 or HPV-012, as compared to an unvaccinated population-based reference cohort of females from Finland. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/02/2023	n/a		
IB/0118/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	13/12/2022	n/a		

	changes to an approved test procedure B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/2325	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	17/11/2022	n/a		
II/0114	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/04/2022	n/a		
IB/0113	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/10/2021	21/09/2022	SmPC and PL	
II/0112/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.4.b - Change to in-process tests or limits	16/09/2021	n/a		

	applied during the manufacture of the AS - Addition of a new in-process test and limits				
WS/1987	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.z - Change in container closure system of the Finished Product - Other variation	11/02/2021	n/a		
IB/0109/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	17/06/2020	n/a		
PSUSA/9175/ 201911	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 2-valent	11/06/2020	n/a		PRAC Recommendation - maintenance
WS/1788/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.2.b - Change in test procedure for an excipient - Deletion of a test procedure if an alternative test	14/05/2020	n/a		

	procedure is already authorised				
II/0106	Update of sections 4.4 and 5.1 of the SmPC based on final results from study HPV-019 listed as a category 3 study in the RMP; this is a safety and immunogenicity study of Cervarix in HIV-positive female subjects aged 15-25 years as compared to quadrivalent HPV, which was assessed in P46/095; and to update section 4.2 of the SmPC to indicate that limited clinical data is now available in 4-6 years old children based on final results from study HPV-073; a phase III, randomised, controlled, single-blind study to evaluate the safety and immunogenicity of Cervarix administered according to an alternative 2-dose schedule (0, 6 month) in 4-6 years old healthy female children, which was assessed in P46/090. The RMP version 22.0 is to be approved including changes to the safety specifications in line with GVP module V revision 2. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	14/05/2020	30/04/2021	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Cervarix EMEA/H/C/000721/II/0106.

IG/1154	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	18/11/2019	n/a		
IA/0104	A.7 - Administrative change - Deletion of manufacturing sites	20/09/2019	n/a		
IB/0103	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/06/2019	n/a		
PSUSA/9175/ 201811	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 2-valent	14/06/2019	n/a		PRAC Recommendation - maintenance
II/0099	Update of section 4.5 of the SmPC in order to reflect the concomitant administration of Cervarix with meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (Nimenrix), based on results from study MENACWY-TT-054. This is a phase III, open, randomised, controlled, multicentre study aimed to assess the immunogenicity and reactogenicity of Nimenrix administered alone as compared to Nimenrix co-administered with HPV vaccine Cervarix or co-administered with Cervarix and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Boostrix) in female adolescents and adults at 9 to 25 years of age; as requested in the CHMP conclusion of procedure P46/093. The Package Leaflet is updated accordingly.	11/04/2019	09/03/2020	SmPC and PL	Section 4.5 of the SmPC was updated to reflect that Cervarix may be administered concomitantly with meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (MenACWY-TT) based on results of study MENACWY-TT-054. The study data demonstrated that Cervarix can be given concomitantly with Nimenrix (MenACWY-TT vaccine) with no impact on the immune response to the human papilloma virus (HPV) 16/18 antigens. In addition, co-administration of Cervarix with Nimenrix and/or Boostrix (diphtheria, tetanus and acellular pertussis (dTpa) vaccine) is well tolerated. The safety and reactogenicity data did not raise any concern. Data also show that co-administration of Cervarix, Nimenrix and Boostrix resulted in lower antibody concentrations against each pertussis antigen compared to co-administration of Cervarix and Boostrix. The immunological interference is not related to co-administration of Cervarix. Despite the

	In addition, the Marketing authorisation holder (MAH) took the opportunity update the package leaflet to correct inconsistencies related to the indication in males. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				failure to meet the non-inferiority criterion, booster response rates and geometric mean concentration fold increase between pre- and post-vaccination time points showed robust responses to each pertussis antigen in both groups.
WS/1529	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	21/03/2019	n/a		
IB/0101	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/02/2019	n/a		
IB/0098	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	10/12/2018	n/a		
WS/1458	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished	18/10/2018	n/a		

	product - Addition of a new test(s) and limits				
PSUSA/9175/ 201711	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 2-valent	14/06/2018	n/a		PRAC Recommendation - maintenance
II/0094	To extend the shelf-life of the finished product pre-filled syringe and vial from 48 to 60 months when stored at 2-8°C. The MAH took the opportunity to update the SmPC, Package Leaflet and labelling to implement QRD template v10, including the standard statement on the Unique Identifier and its carrier. In addition, some minor editorial changes are made and the list of local representatives in the Patient Leaflet has been updated. B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	17/05/2018	11/04/2019	SmPC, Labelling and PL	
IG/0921	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	08/05/2018	n/a		
IG/0915	B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of	26/04/2018	n/a		

	a Member State - Excipient/AS starting material				
II/0085	Submission of Study EPI-HPV-069, a meta-analysis assessing the risk of three autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre Syndrome (GBS) and Inflammatory Bowel Disease (IBD). The EPI-HPV-069 study is a post-authorisation commitment of the marketing authorisation (PASS register number EUPAS13332). An updated RMP (version 20) is approved, including changes related to the EPI-HPV-069 meta-analysis submitted and minor updates related to other studies. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/03/2018	n/a		
IB/0092	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	12/12/2017	n/a		
IB/0091	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	29/11/2017	n/a		
WS/1183	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.i - Change in the specification parameters and/or limits of an AS, starting	05/10/2017	n/a		

	material/intermediate/reagent - Where there is no monograph in the European/National Ph. for the AS, a change in specification from in-house to a non-official/third country Ph.				
IG/0811	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	19/06/2017	n/a		
II/0088	Submission of the final report from the pregnancy registry data (study EPI-HPV-067); this study is a Post Authorisation Safety Study (PASS), and information related to the use of Cervarix during pregnancy was identified as important missing information in the Risk Management Plan (RMP). The requested variation proposed no amendments to the Product Information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/06/2017	n/a		
PSUSA/9175/ 201611	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 2-valent	09/06/2017	n/a		PRAC Recommendation - maintenance
II/0081	To submit final study results of a clinical study. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/03/2017	n/a		

II/0086	Submission of the final report from study HPV-039, listed in the RMP as one of the measures to bring additional information on the theoretical risk of acquiring vaccine-induced autoimmune diseases and on pregnancy outcomes after vaccination. With this submission the MAH fulfils post-authorisation measure MEA 081. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/03/2017	n/a		
II/0080	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/02/2017	24/01/2018	SmPC	The purpose of this variation was to fulfil a Post-Authorization Measure by submitting the results of long-term follow up (10 years post-vaccination) data from study HPV-060. The information on seropositivity for HPV-16 and HPV-18 up to 18 months after primary vaccination in study HPV-014 contained in the SmPC was replaced with more detailed information on the geometric mean titers (GMT) up to 10 years from the extension study HPV-060, to add the results of the long-term persistence study in section 5.1 of the SmPC, in subsection "Persistence of Immune Response to Cervarix".
II/0075	Update of section 5.1 of the SmPC with wording on the clinical efficacy of Cervarix in women aged 26 years and older, based on the submission of the final report for study HPV-015 (MEA 083); this is a phase III, double-blind, randomized, controlled study to evaluate the safety, immunogenicity and efficacy of HPV16/18 L1/AS04 vaccine administered	23/02/2017	24/01/2018	SmPC	The efficacy of Cervarix was assessed in a double-blind, randomised Phase III clinical trial (HPV-015) that included a total of 5778 women aged 26-72 years (median: 37.0 years). Final analysis was performed at study conclusion, 7 years after 1st vaccination. At final analysis at 84 months post-vaccination (M84), a new medical review of new onset of adverse events collected up to 48 months post-

	intramuscularly according to a three-dose schedule (0, 1, 6 month) in healthy adult female subjects aged 26 years and above. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				vaccination (M48) was performed at M84. An additional analysis on potential immune mediated diseases and pregnancy outcomes collected at M48 was also done at M84. The primary endpoint of study HPV-105 was a combination of a virological and a histopathological endpoint: human papilloma virus types (HPV-16/18) related 6 month persistence infection and/or cervical intraepithelial neoplasia (CIN1+). The primary analyses of efficacy were performed on the according to protocol (ATP) cohort for efficacy and the total vaccinated cohort (TVC) which included a subset of up to 15% of women with a history of human papilloma virus (HPV)-associated infection or disease (defined as two or more abnormal smears in sequence, abnormal colposcopy, or biopsy or treatment of the cervix after abnormal smear or colposcopy findings). Inclusion of this subset allowed assessment of prophylactic efficacy in a population that is thought to reflect a real-world setting, as adult women are the age group generally targeted for cervical screening. There is no evidence whether prevention of persistent infection that lasts for at least 6 months is a relevant surrogate marker for cervical cancer prevention in women aged 26 years and above. Amongst the adverse drug reations reported from study HPV-015 and present at a higher frequency in Cervarix than in control group, all were already listed or can be linked to already listed terms. All terms already listed were reported at frequencies inferior or equal to those currently reported in the SmPC. Overall, No new safety signals were observed.

WS/1009	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.z - Change in test procedure for the finished product - Other variation	10/11/2016	n/a		
IG/0719/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	21/09/2016	n/a		
IA/0082	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished	20/09/2016	n/a		

	product - Addition of a new test(s) and limits				
II/0067	Extension of Indication to include prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1 and 6.3 of the SmPC are updated. The Package Leaflet and the RMP (final version 17.0) are updated in accordance. In addition the MAH took the opportunity to implement QRD version 9.1 in the product information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/06/2016	29/07/2016	SmPC, Annex II, Labelling and PL	Please refer to the published Assessment Report Cervarix H-C-721-II-67-AR.
PSUSA/9175/ 201511	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 2-valent	09/06/2016	n/a		PRAC Recommendation - maintenance
IG/0679	B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	01/06/2016	n/a		
WS/0843	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.2.z - Change in test procedure for an excipient - Other variation	21/04/2016	n/a		

WS/0864	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	25/02/2016	n/a		
A20/0071	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 09 July 2015 the opinion of the European Medicines Agency on whether there is evidence of a causal association between HPV vaccination and CRPS and/or POTS, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures on the marketing authorisations concerned. As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.	19/11/2015	12/01/2016		Please refer to the assessment report: Cervarix: EMEA/H/A20/1421/C/0721/0071 Gardasil: EMEA/H/A20/1421/C/0703/0060 Gardasil 9: EMEA/H/A20/1421/C/3852/0001 Silgard: EMEA/H/A20/1421/C/0732/0054
IB/0074/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the	16/12/2015	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0069	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/11/2015	n/a		
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/11/2015	10/12/2015	PL	
WS/0817/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for	29/10/2015	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place				
II/0070	Submission of study EPI-HPV-033 "surveillance report from the HIV/STI department, public health England centre for infectious disease surveillance & control (CIDSC) regarding the impact of the English HPV immunisation programme using Cervarix vaccine" in fulfilment of MEA078. No changes in the PI have been proposed. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/09/2015	n/a		
WS/0734	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.z - Change in control of excipients in the Finished Product - Other variation	25/06/2015	n/a		
PSUSA/9175/ 201411	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 2-valent	11/06/2015	n/a		PRAC Recommendation - maintenance
II/0066/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for	23/04/2015	n/a		

	biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				
II/0061	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	10/12/2015	SmPC and PL	
IB/0064/G	This was an application for a group of variations. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation	18/12/2014	n/a		
II/0058	Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) for Cervarix to extend the existing 0, 6 months vaccination schedule to a flexible 0, 5-13 months schedule in girls aged 9-14 years old. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	21/11/2014	SmPC and PL	The purpose of this variation is to update the SmPC for Cervarix with a flexible 2-dose schedule (0, 5-13 months) in females aged 9-14 years old. In support of this variation application, results from the ongoing study HPV-070 up to Month 13 (six months post last vaccination in 2-dose [0,6-month] and 3-dose [0,1,6-month] groups and one month post last vaccination in the 2-dose [0,12-month] group) have been submitted . Study HPV-070 is a phase IIIb, open-label, randomised, age-stratified, multi-centre trial designed to assess the

					immunogenicity and safety of Cervarix when administered according to alternative 2-dose schedules (0, 6 or 0, 12 months) in 9-14 years old healthy females compared to a standard 3-dose schedule of Cervarix in 15-25 years old healthy females. The acceptability of a 2-dose schedule for Cervarix was previously evaluated and approved based in the results of the proof-of-concept study HPV-048 and study HPV-070 (with data up to week 7). Based on the available data, the CHMP endorsed in this variation the introduction of a flexible 2-dose schedule (0, 5-13 months) in females aged 9-14 years. However, demonstrating persistent clinical protection (e.g. against persistent infection and premalignant lesions) among 9-14 years old girls vaccinated with the 2-dose schedule remains a major challenge. The value of statistical modeling in predicting antibody concentrations up to 20 years, or beyond, after the first vaccine dose remains unknown. To address this, the MAH previously committed to perform an observational trial in the context of the previously approved 2-dose schedule of 0, 6 months. The CHMP was of the view that other options should be explored so as to address potential immunogenicity waning and/or demonstration of persistent clinical protection with the new, flexible 2-dose schedule. These issues are addressed and under assessment in dossier EMEA-H-C-721-REC 076. The benefit-risk balance of Cervarix remains positive.
WS/0591	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/11/2014	n/a		

	Submission of final study report of a post-approval clinical study to compare the current and the new plunger stoppers and tip caps in response to a CHMP recommendation. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0063	To delete the sentence "The decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her potential benefit from vaccination." in section 4.4 Special warnings and precautions in the Summary of Product Characteristics (SmPC), to reflect the outcome of the FUM036.1 assessment as adopted by the CHMP. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/08/2014	21/11/2014	SmPC	
IG/0467	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	20/08/2014	n/a		
WS/0515	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	26/06/2014	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/0426/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	26/06/2014	n/a		
IG/0446	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	24/06/2014	n/a		
PSUV/0055	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance
WS/0497	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.2.a - Change in test procedure for an excipient	25/04/2014	n/a		

	- Minor changes to an approved test procedure				
WS/0496	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	25/04/2014	n/a		
II/0048	Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) for Cervarix to include a reduced 2-dose schedule (0, 6 months) in females aged 9-14 years old. The MAH took the opportunity to add Croatia to the list of representatives. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	18/12/2013	SmPC and PL	Following the immunogenicity results in the proof-of-concept study HPV-048 showing that a 2-dose schedule of Cervarix administered at 0, 6 months in 9-14 years old females was non-inferior to the standard 3-dose schedule in females aged 15-25 years, the MAH conducted study HPV-070 as a phase III confirmatory immunobridging study. Efficacy data in subjects receiving 2-doses of Cervarix in 2 large phase III studies (studies HPV-008 and HPV-009) was provided as supportive evidence, along with data obtained from the surveillance of HPV-specific infection after introduction of the National HPV Immunisation Program in the UK in girls aged 12-13 years. The overall immunogenicity and safety data provided demonstrate the non-inferiority of a 0, 6 months schedule in 9-14 years old girls vs. the standard 3-dose schedule. The 2-dose schedule using an interval of 5 to 7 months provides a suitable alternative to the 3-dose schedule as it may improve the vaccine’s coverage.

IA/0052	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/11/2013	n/a		
IB/0051	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	22/11/2013	n/a		
WS/0443	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	24/10/2013	n/a		
IA/0050	A.7 - Administrative change - Deletion of manufacturing sites	26/09/2013	n/a		
II/0038	Update of sections 4.4, 4.8 and 5.1 of the SmPC to include immunogenicity data based on Month 12 final analysis of the study HPV-020. The Package Leaflet was updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	27/06/2013	18/12/2013	SmPC and PL	Effectiveness of Cervarix female subjects 18-25 years of age with asymptomatic HIV infection has been evaluated in Study HPV-020. Study results showed that Cervarix is immunogenic and generally well tolerated when administered to 18-25 years old women infected with HIV infection. All subjects developed immune responses to both HPV 16 and 18 which was maintained up to a follow-up period of 12 months. The achieved titers appeared to be lower in the HIV infected group and the clinical relevance of this observation remains unknown. Information about protection against persistent infection or precancerous

					lesions among HIV infected women is still missing.
IG/0306	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2013	n/a		
IB/0045	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	30/04/2013	n/a		
IG/0297	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2013	n/a		
II/0036	Update of sections 4.1 and 5.1 of the SmPC with prophylactic efficacy data against premalignant vulvar and vaginal lesions. The Package Leaflet is updated in accordance. Changes in the Annex II regarding Pharmacovigilance system, PSUR and RMP were introduced. The MAH took the opportunity to update the "Information intended for healthcare professionals" with thermostability wording for the 2-dose vial. Furthermore, the MAH took the opportunity to update the local representatives of Cyprus in the Package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	27/03/2013	SmPC and PL	Please refer to the assessment report from variation II/36.
IG/0265/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons	28/01/2013	n/a		

	or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
WS/0336	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To introduce a new method for monitoring homogeneity during filling. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	17/01/2013	n/a		
IB/0043	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol	11/12/2012	27/03/2013	SmPC	
WS/0304	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To introduce an additional method for identification of the Master and Working Seeds used for the	18/10/2012	18/10/2012		

	manufacture of MPL. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS				
R/0035	Renewal of the marketing authorisation.	19/07/2012	17/09/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Cervarixl continues to be favourable. The CHMP recommends the renewal of the marketing authorisation for Cervarix with unlimited validity.
II/0034	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	17/09/2012	SmPC and PL	Data from the interim analysis of a Phase III clinical trial (HPV-015) was evaluated within this procedure. Vaccine efficacy was demonstrated in women 26 year and older against 6 month persistent infection and/or CIN1+ associated with HPV16/18 infection in both the ATP and TVC cohorts. Cross protection, measured as significant vaccine efficacy against 6 month persistent infection, was demonstrated against HPV-31 and HPV-45 in the ATP cohort, and with regard to immunogenicity, seropositivity was demonstrated at month 48 for HPV-16 and HPV-18 in the initially seronegative population. These data showed the overall efficacy of Cervarix in women 26 years and older. At the 48-month time point, i.e. 42 months after completion of the full vaccination course, 100% and 99.4%

					of initially seronegative women of 26 years or older remained seropositive for anti-HPV-16 and anti-HPV-18 antibodies, respectively. The large sample size of study HPV-015 allowed to perform detailed evaluations of safety- related outcomes in the new population investigated, and to compare the safety profile of the vaccine in older subjects with that in women aged 15-25 years. In conclusion, HPV-015 study results confirmed the vaccine efficacy as well as immunogenicity. No new safety signals were observed.
IA/0039/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	20/06/2012	17/09/2012	Annex II	
IG/0170/G	This was an application for a group of variations. B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	25/04/2012	n/a		
WS/0239	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	19/04/2012	n/a		

	Registration of an additional site for QC sterility testing activities for pre-filled syringes, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The batch release site remains unchanged. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
WS/0201/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To propose new target fill volume controls. To align the volume specifications to be applied at release and during stability evaluation. To revise QC release procedures for final container volume determination. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	19/01/2012	n/a		

	procedure				
II/0022	Update of Summary of Product Characteristics Update of Section 5.1 "Pharmacodynamic Properties" of the Summary of Product Characteristics (SmPC) to include the long term immunogenicity data based on the month 36 final analysis of the study HPV-023, which is the long-term follow-up for up to 9.4 years (113 months) of vaccine efficacy, immunogenicity and safety of the primary study, HPV-001. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	05/12/2011	SmPC	Overall, in study HPV-023 and also in the combined (pooled) analysis, the vaccine efficacy was in general similar or higher in the Total cohort than in the ATP cohort, mostly due to a higher incidence of cases in the placebo group. An overall efficacy against non-vaccine types could not be demonstrated due to the limited sample size and low prevalence of non-vaccine subtypes. HPV 023 long term study results showed high and sustained immunogenicity over 113 months of follow-up for both anti-HPV-16 and anti-HPV-18 antibodies. No safety signals were identified during the course of Study HPV-023. The safety analysis did not show any clinically relevant differences between the vaccine and control groups indicating that Cervarix has an acceptable long-term safety profile.
II/0021	Update of Summary of Product Characteristics and Package Leaflet Update of the Summary of Product Characteristics (SmPC) for Cervarix with data obtained in subjects of 9 years of age and to extend the current indication as from 9 years. The Package leaflet was updated accordingly. Update of local representatives. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/10/2011	05/12/2011	SmPC and PL	Please refer to the Assessment Report for variation II/21.
IG/0133	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	22/11/2011	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
WS/0166	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Registration of an additional facility for filling of finished product. The change relates to pre-filled syringes only. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.	20/10/2011	20/10/2011		
II/0020	Update of the efficacy and immunogenicity data in Section 5.1 "Pharmacodynamic Properties" of the SmPC for Cervarix based on the data from the end-of-study analysis of study HPV-008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	26/08/2011	SmPC	Data from the end-of-study analysis of study HPV-008 strengthens and confirms the efficacy, immunogenicity and safety of the Cervarix. The overall impact of vaccination observed at final analysis was confirmed at the-end-of study analysis. Additional data were available for cross-protection against other oncogenic HPV types, which generally confirmed the results observed at final analysis. No clinically differences in overall safety outcomes have been identified and compliance with the full vaccination course was equally high between treatment groups. The end-of-study analysis provides longer follow-up data and the risk/benefit balance of Cervarix remains favourable.
IG/0081	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the	07/07/2011	n/a		

	back-up procedure of the QPPV				
IG/0080	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	01/07/2011	n/a		
IG/0064/G	This was an application for a group of variations. Update of section 4.8 of the SmPC to include immediate injection site pain, stinging and burning sensation. The PL is updated in accordance. The MAH has also taken the opportunity to align section 4.6 of the prefilled syringe presentation with the vial presentation. Furthermore, the Labelling is updated to specify the container 'prefilled syringe'. In addition, the MAH has taken the opportunity to update the list of local representatives in the PL. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test	04/05/2011	n/a		Following clusters of spontaneous reports of immediate onset injection site pain reported in certain batches of the preservative-free formulation of Twinrix Adult, immediate pain, stinging and burning at the injection site has been reflected in section 4.8 of the SmPC and section 4 of the package leaflet. The MAH's investigation report revealed no specific root cause for the clusters of reports of immediate injection site pain. The injection site reactions were non-serious and self-limited in all cases. The benefit-risk of Twinrix Adult remains positive.

	procedure is already authorised B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
IG/0062/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	27/04/2011	n/a		
IG/0052/G	This was an application for a group of variations. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding	18/03/2011	n/a		

	test method B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0019	Update of Summary of Product Characteristics and Package Leaflet Update of the section 4.5 of the SmPC and section 2 of the Package leaflet based on data from study HPV-030 to evaluate the immunogenicity and safety of HPV-16/18 L1 VLP AS04 vaccine (Cervarix) when co-administrated with the Hepatitis B vaccine (Engerix-B) in healthy female subjects aged 9-15 years. The package leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	21/02/2011	SmPC and PL	HPV-030 was a phase IIIb, randomized, open, multicentre study designed to evaluate the immunogenicity and safety of Cervarix coadministered with Engerix-B in healthy female subjects aged 9-15 years. Non-inferiority of the immune response induced by co-administration of Cervarix and Engerix B was demonstrated compared to their separate administration. This information has been reflected in the product information.
II/0018	Update of SmPC and Annex II Update of long-term immunogenicity data in Section 5.1 of the SmPC based on the month 24 interim analysis of the study HPV-023, which is the long-term follow-up for up to 8.4 years (100.8 months) of vaccine efficacy, immunogenicity and safety of the primary study, HPV-001. Annex II is updated to delete the reference made to the version number of the Detailed Description of the Pharmacovigilance System.	20/01/2011	21/02/2011	SmPC	Study HPV-023 is a three year additional follow-up of vaccine efficacy and immunogenicity in the Brazilian cohort of subjects who had previously been vaccinated with three doses of Cervarix in study HPV-001 and who had been followed-up in study HPV-007. In study HPV- 023 the immune response continued to be evaluated up to 101 months. 87 subjects in the vaccine group had immunogenicity data after the first vaccine dose with a median follow-up of 7.9 years. In this context the study provided evidence of a sustained immune response against

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				HPV-16 and HPV-18, both in ELISA and PBNA testing.
II/0017	Update of section 4.2 with regards to flexibility in the administration of the third dose on the basis of results from study HPV-044. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	06/08/2010	SmPC	Study HPV-044 is a phase IIIb open, randomised multi-centre study investigating an alternative schedule of the third dose of Cervarix. Based on the results of the study it was concluded that the third dose of Cervarix can be offered any time between 65 and 12 months after the administration of the first dose.
II/0016	Update of Summary of Product Characteristics To update section 5.1 of the SmPC based on data from study HPV-024 which addressed immunogenicity, reactogenicity and safety of a challenge dose of Cervarix. Update of Summary of Product Characteristics	24/06/2010	06/08/2010	SmPC	In study 024 (a subset of study 001/007), a challenge dose of Cervarix was administered to 65 subjects at a mean interval of 6.8 years after the administration of the first vaccine dose. An anamnestic immune response to HPV-16 and HPV-18 (by ELISA) was observed one week and one month after the challenge dose, GMTs one month after the challenge dose exceeded those observed one month after the primary 3-dose vaccination.
II/0011	To update sections 4.1, 4.4, 4.6 and 5.1 of the SmPC with the final analysis of pivotal study HPV-008. The PL was revised accordingly. Annex II was revised with the updated risk management plan approved. Update of Summary of Product Characteristics and Package Leaflet	24/06/2010	06/08/2010	SmPC and PL	Please refer to the scientific discussion: Cervarix-H-721-II-11-AR
II/0015	Update section 5.1 of the SmPC based on the results of a study (HPV-023) on long-term follow-up for up	22/04/2010	02/06/2010	SmPC	The MAH based on the results of a study (HPV-023) on long-term follow-up for up to 7,4 years of vaccine efficacy,

	to 7,4 years of vaccine efficacy, immunogenicity and safety of the primary study, HPV-001. Update of Summary of Product Characteristics				immunogenicity and safety of the primary study HPV-001, wanted to update the section 5.1 of the SmPC due to new immunogenicity data. In study 023, 111 subjects in the vaccine group had immunogenicity data at the [M83-M88] interval after the first vaccine dose with a median follow-up of 7 years. Of these subjects, 100% remained seropositive for HPV-16 and HPV-18. Furthermore vaccine-induced IgG GMTs for both HPV-16 and HPV-18 peaked at month 7 and then declined to reach a plateau from month 18 up to the [M83-M88] interval with ELISA GMTs for both HPV-16 and HPV-18. In conclusion, these results confirm a sustained immunologic response of the vaccine.
II/0014	Change in cell identity method. Change to the test procedure and/or specification of a raw material	17/12/2009	06/01/2010		
II/0013	Update of Summary of Product Characteristics and Package Leaflet To update section 4.4 of the SPC to include a warning on syncope and to update section 4.8 of the SPC to include allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema and syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements, as undesirable effects observed during postmarketing surveillance, following evaluation of the periodic safety update report (PSUR). The MAH also took this opportunity to update section 6.6 of the pre-filled syringes SPC to include further	22/10/2009	23/11/2009	SmPC and PL	The following adverse reactions have been reported during post-marketing experience: allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema, lymphadenopathy and syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements. Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. A warning was included to alert health care professionals to put procedures in place to avoid injury

	instructions for the use of the pre-filled syringe (with illustration). Consequently, the package leaflet has been updated in section 4 to reflect the above undesirable effects and in section 6 (only for pre-filled syringes) to reflect the illustrated handling instructions. Update of Summary of Product Characteristics and Package Leaflet				from faints.
II/0012	Update of Summary of Product Characteristics and Package Leaflet To update section 4.5 of the SPC with Month 7 data of the study HPV-029 concerning the concomitant administration of Cervarix with a combined hepatitis B (inactivated) and hepatitis B (rDNA) vaccine (HAB vaccine). Section 2 of the PL was updated accordingly. This submission fulfils a follow up measure. The MAH took the opportunity of this variation to update the contact details for the local representative in Denmark. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	23/11/2009	SmPC and PL	To evaluate the feasibility of co-administration of Cervarix and a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (HAB vaccine) a trial was ran to assess the impact immunogenicity, reactogenicity and safety, as compared to their separate administration, in healthy female subjects aged between 9 and 15 years of age. Results show that Cervarix may be administered concomitantly with a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (HAB vaccine). Administration of Cervarix at the same time as Twinrix (HAB vaccine) has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody titers were lower on co-administration, but the clinical significance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs ? 10mIU/ml was 98.3% for concomitant vaccination and 100% for Twinrix alone.
II/0006	Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	24/07/2009	SmPC and PL	At the time of the marketing authorisation the MAH has committed to perform study HPV 042 to investigate safety and immunogenicity of the coadministration of Cervarix

	To update section 4.5 of the SPC with Month 7 data of the study HPV-042 on the concomitant administration of Cervarix with the combined diphtheria, tetanus, pertussis and/or poliomyelitis booster vaccine. Section 2 of the PL was updated accordingly. This submission fulfils FUM 031. Update of Summary of Product Characteristics and Package Leaflet				with the combined diphtheria, tetanus, pertussis and/or poliomyelitis booster vaccine (dTpa-IPV vaccine) in female subjects aged 10-18 years. The MAH has provided results obtained after 7 months of the study. The results show that Cervarix can be administered concomitantly with a combined booster vaccine containing diphtheria, tetanus and pertussis [acellular] with or without inactivated poliomyelitis, (dTpa, dTpa-IPV vaccines), with no clinically relevant interference with antibody response to any of the components of either vaccine. Safety data obtained in this study does not indicate a deterioration of the safety profiles of both vaccines if given concomitantly or in a sequential way. If Cervarix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at a separate injection site (another part of your body, e.g. the other arm) during the same visit.
II/0007	Change to the primary pack stopper and tip cap for pre-filled syringes. Change(s) to the manufacturing process for the finished product	25/06/2009	06/07/2009		
II/0008	Change to the manufacturing process for the active substance Change(s) to the manufacturing process for the active substance	29/05/2009	11/06/2009		

IB/0009	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	05/05/2009	n/a		
II/0005	Changes in shelf life of drug product. Change(s) to shelf-life or storage conditions	19/03/2009	22/04/2009	SmPC, Annex II, Labelling and PL	
IA/0010	IA_09_Deletion of manufacturing site	14/04/2009	n/a		
II/0004	The Marketing Authorisation Holder applied to add a two dose multidose presentation (1.0ml without preservative) in packs of 1, 10 and 100 to the existing range of presentations. New presentation(s)	23/10/2008	26/11/2008	SmPC, Labelling and PL	
II/0002	The Marketing Authorisation Holder applied to scale up the manufacture of adjuvant MPL liquid bulk. Change(s) to the manufacturing process for the active substance	25/09/2008	03/10/2008		
II/0001	To update section 5.1 of the SPC, with Month 36 analysis of efficacy and immunogenicity data from study HPV-007, to fulfil FUM 15. Furthermore, the pharmaco-therapeutic group wording is updated to "Papillomavirus vaccines". Upon CHMP request section 4.1 is simplified to be in line with the wording of HPV vaccines adopted by CHMP in May 2008. In addition, the MAH takes the opportunity to include	26/06/2008	13/08/2008	SmPC, Labelling and PL	The MAH provided additional follow up (Month 36 analysis) efficacy and immunogenicity data from the long-term follow-up of the primary efficacy study HPV-001 in study HPV-007. The final results from Study HPV-007 show that Cervarix vaccine efficacy against 12-month persistent infection associated with types HPV-16 and HPV-18 is maintained for up to 6.4 years after the first vaccine dose. In addition, the vast majority (approximately 99% of subjects) remain

	the Marketing Authorisation Numbers in section 8 of the SPC and in section 12 of the Labelling, as well as the date of the first authorisation in section 9 of the SPC. Section 2 of the PL is updated accordingly. PL is updated to include a change in the local representative for Latvia. Update of Summary of Product Characteristics, Labelling and Package Leaflet				seropositive for HPV-16 and HPV-18 (as measured by ELISA) up to 76 months following the first vaccine dose ensuring duration of persistence of the immune response to vaccine types HPV-16 and HPV-18. No relevant differences were observed in the safety profile between vaccine and placebo groups.
IA/0003	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	13/05/2008	n/a		