Gardasil

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
IAIN/0108	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/10/2024		SmPC and PL	
IB/0106	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	28/08/2024	n/a		

[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).

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IB/0105	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	26/03/2024	n/a		
IB/0104/G	This was an application for a group of variations. 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 the AS -replacement or addition of a site where batch control/testing takes place B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	26/03/2024		SmPC, Annex II and PL	
IB/0103	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	05/02/2024	n/a		
IB/0102	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	08/04/2023	n/a		
PSUSA/1634/ 202205	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 4-valent	12/01/2023	n/a		PRAC Recommendation - maintenance
WS/2336	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC to add the effect of vaccination campaigns on the reduction in the	13/10/2022	17/07/2023	SmPC	The following wording about the effect of vaccination campaigns on the reduction in the incidence of Juvenile-onset Recurrent Respiratory Papillomatosis (JoRRP) based upon published observational studies was agreed for addition to SmPC section 5.1: "JoRRP is caused by upper airway infection primarily with

	incidence of Juvenile-onset Recurrent Respiratory Papillomatosis (JoRRP) based upon published observational studies. In addition, the MAH took the opportunity to introduce minor editorial changes to the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				HPV types 6 and 11, acquired vertically (mother-to-child) during childbirth. Observational studies in the US and Australia have shown that the introduction of Gardasil since 2006 has led to declines in the incidence of JoRRP at population level.”
IG/1529/G	This was an application for a group of variations. 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.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) 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	06/07/2022	17/07/2023	Annex II	
IB/0097	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/06/2022	n/a		

IB/0098	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/06/2022	n/a		
T/0096	Transfer of Marketing Authorisation	14/03/2022	29/04/2022	SmPC, Labelling and PL	
IB/0095	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	04/01/2022	29/04/2022	SmPC, Labelling and PL	
IB/0094	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	05/10/2021	n/a		
N/0093	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/10/2021	15/11/2021	PL	
WS/2037	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.2 - Introduction of a post approval change management protocol related to the AS	24/06/2021	n/a		
II/0091	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/04/2021	n/a		
II/0087	Update of section 5.1 of the SmPC in order to update the information of the duration of immunity following	06/11/2020	15/11/2021	SmPC, Annex II, Labelling	Update of section 5.1 of the SmPC in order to update the information of the duration of immunity following a 2-dose

	a 2-dose schedule of Gardasil based on the results from extension Protocol V501-167; this was a randomized clinical trial that assessed the immunogenicity of a 2 dose schedule of Gardasil in adolescents 9 to 13 years of age compared to a 3-dose schedule in young women 16 to 26 years of age and also compared to a 3 dose schedule of the Gardasil in adolescents 9 to 13 years of age. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			and PL	schedule of Gardasil based on the results from extension Protocol V501-167; this was a randomized clinical trial that assessed the immunogenicity of a 2 dose schedule of Gardasil in adolescents 9 to 13 years of age compared to a 3-dose schedule in young women 16 to 26 years of age and also compared to a 3 dose schedule of the Gardasil in adolescents 9 to 13 years of age . In addition, the MAH is taking the opportunity update the product information in line with the Excipients guideline (SANTE-2017-11668) and the Guideline on quality aspects included in the product information for vaccines for human use (EMA/CHMP/BWP/133540/2017). Furthermore, the PI is being brought in line with the latest QRD template (version 10.1) and some minor editorial changes regarding the nomenclature for excipients have been implemented.
II/0089/G	This was an application for a group of variations. 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.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	29/10/2020	n/a		
II/0086	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	03/09/2020	n/a		
IAIN/0090	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	02/09/2020	n/a		

	site				
IB/0088/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	30/07/2020	n/a		
N/0084	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/02/2020	15/11/2021	PL	
IB/0085	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	10/02/2020	n/a		
PSUSA/1634/ 201905	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 4-valent	16/01/2020	n/a		PRAC Recommendation - maintenance
IB/0082/G	This was an application for a group of variations. B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	20/09/2019	n/a		
II/0081	Update of the RMP to version 14.0 to update the list of safety concerns by removing the important	16/05/2019	n/a		

	identified risks syncope with fall resulting in injury, the important potential risks: viral type replacement and convulsion, and the missing information: immunogenicity, unanticipated safety signals and long-term safety, and in order to incorporate information from completed category 3 post-approval measure and scientific information on the safety profile of the qHPV vaccine. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
II/0080	Update of sections 4.4 and 5.1 of the SmPC in order to update the information related to the effectiveness and immunogenicity of the immune response of Gardasil, based on the final results from the long-term follow-up of study V501-P015-21 listed as a category 3 study in the RMP; this study was designed to evaluate the effectiveness, immunogenicity and safety of the quadrivalent human papillomavirus (qHPV) vaccine for at least 10 years; the Package Leaflet is updated accordingly. The RMP version 12.1 is approved in line with the GVP Module V (Rev 2). The MAH is taking the opportunity to implement minor editorial changes in the product information.	14/03/2019	12/06/2019	SmPC, Labelling and PL	The final results from the long-term follow-up of study V501-P015-21 have shown duration of immunity for human papillomavirus (HPV) 6, 11, 16, and 18, following a 3-dose series up to 14 years post-vaccination in women between 16 to 23 years of age. The results have shown that anti-HPV 6, 11, 16, 18 geometric mean titres (GMTs), peaked at Month 7 post-vaccination, gradually declined through Month 24, and were generally stable thereafter, remaining above the serostatus cut-offs through Month 168. The percentage of subjects remaining seropositive through Month 168 remained >90% for HPV types 6, 11, and 16, and 52% for HPV type 18, when assessed by competitive Luminex Immunoassay (cLIA). At Month 168, the seropositivity rates, as assessed by IgG LIA (a more sensitive assay that measures all IgG

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				antibodies produced in response to vaccination) were >90% for all HPV types.
PSUSA/1634/ 201805	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 4-valent	17/01/2019	n/a		PRAC Recommendation - maintenance
II/0078	To introduce a post-approval change management protocol for the finished product to include Patheon Italia S.p.A (Viale G.B. Stucchi 110, 20900 Monza (MB), Italy) as an additional manufacturing and quality control site. The PAMCP applies only to the vials presentation (EU/1/06/357/001,002 and 018). B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	26/07/2018	n/a		
II/0077	Changes in the manufacturing process of the active substance (Human Papillomavirus Vaccine [Types 6-11-16-18] (Recombinant, adsorbed), specifically the HPV 16 L1 protein) to increase the lifetime of filters membranes and chromatography resins. The requested variation proposed no amendments to the Product Information. 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	26/07/2018	n/a		

WS/1349/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. Update of section 5.1 of the SmPC in order to update the information following final results from two Long-term follow-up (LTFU) studies: - Protocol V501-020-21, a category 3 study part of the pharmacovigilance activities foreseen in the Risk Management Plan (RMP) of the qHPV vaccine. It is an extension of study V501-020 (the pivotal efficacy study of qHPV vaccine in young men 16 to 26 years of age) to assess effectiveness and immunogenicity of the qHPV vaccine for up to 10 years of follow-up. Submission of this final report fulfils Gardasil MEA 070.3 and Silgard MEA 069.3. - Extension of Protocol V501-16. The base study was an MSD-sponsored randomized clinical trial that assessed the immunogenicity of a 2 dose Schedule of the qHPV in adolescents 9 to 13 years of age compared to a 3-dose schedule in young women16 to 26 years of age. The study provides additional immunogenicity follow-up through 5 years post-vaccination. Submission of this study fulfils Gardasil REC 083 and Silgard REC 080. RMP version 12 was also submitted, updated to reflect completion of the above-mentioned category 3 study.	17/05/2018	12/06/2019	SmPC, Labelling and PL	Based on the final results from two Long-term follow-up clinical studies (V501-020-21 and V501-16), Section 5.1 of the SmPC was amended to update figures and reflect effectiveness and sustained immunogenicity of qHPV vaccine when administered in young men 16 to 26 years of age. Additionally, the relevant sub-section was updated to include a paragraph on sustained immunogenicity following administration of a 2-dose series of qHPV vaccine in girls 9 to 13 years of age.

	In addition, the Worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD template version 10 and to amend the details of one local representative in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0075	Introduction of a post-approval change management protocol (PACMP) intended to add Baxter Pharmaceuticals Solutions LLC in Bloomington, IN, USA as a manufacturing and testing site related to the Human Papillomavirus (Types 6, 11, 16, 18) recombinant vaccine (GARDASIL) finished product. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	15/03/2018	n/a		
PSUSA/1634/ 201705	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 4-valent	11/01/2018	n/a		PRAC Recommendation - maintenance
WS/1126	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.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is	21/04/2017	n/a		

	increased/decreased without process change (e.g. duplication of line)				
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/04/2017	20/12/2017	PL	
WS/1128	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC following/based on the final report for Study P019-21 (Gardasil MEA 060.2 and Silgard MEA 059.2) and fourth interim report for Study P015-21 (Gardasil/Silgard MEA 019.7). Study P019-21 is a long-term Follow-up Study of Safety, Immunogenicity, and Effectiveness of Gardasil (Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine) in Mid-Adult Women - The FUTURE III (Females United to Unilaterally Reduce Endo/Ecto Cervical Cancer). Study P015-21 is a registry-based Study of Protocol V501-015. Subjects and Recipients of Gardasil recombinant vaccine in Countries with centralized cervical cancer screening infrastructures to evaluate the long-term effectiveness, immunogenicity and safety of Gardasil. The RMP version 11 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	20/12/2017	SmPC	SmPC section 5.1 was updated with latest data/figures from long-term follow-up studies P019-21 and P015-21, part of the development plan and are post-authorisation measures in the Risk Management Plan (RMP) for qHPV. The generated data and supportive data from other long-term follow-up studies on effectiveness and immunogenicity supports that the benefit risk balance remains positive. No new safety signal was detected.

IG/0777	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2017	20/12/2017	SmPC, Labelling and PL	
PSUSA/1634/ 201605	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 4-valent	12/01/2017	n/a		PRAC Recommendation - maintenance
IG/0758	A.1 - Administrative change - Change in the name and/or address of the MAH	11/01/2017	16/02/2017	SmPC, Labelling and PL	
N/0068	Update of the package leaflet with revised contact details of the local representatives. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2016	16/02/2017	PL	
WS/0908	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Section 5.1 of the SmPC with long-term data based on the final clinical study report for study P018-11 and interim reports for studies P015-21, P019-21 and P020-21; in addition, the MAH took the opportunity to bring the PI in line with the QRD template version 9.1 and to combine the SmPC of the pre-filled syringe and the vial presentations. Furthermore, section 4.4 has been amended to clarify the sentence regarding the interchangeability of Gardasil/Silgard with other HPV vaccines. RMP version 10.0 was provided as part of the application	01/04/2016	16/02/2017	SmPC, Annex II and Labelling	

	and is considered acceptable. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/0910	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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	17/03/2016	n/a		
WS/0895	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	11/02/2016	16/02/2017	SmPC and PL	
PSUSA/1634/ 201505	Periodic Safety Update EU Single assessment - human papillomavirus vaccine (rDNA) - 4-valent	14/01/2016	n/a		PRAC Recommendation - maintenance
A20/0060	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	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

	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.				
IA/0064	A.7 - Administrative change - Deletion of manufacturing sites	21/12/2015	n/a		
IG/0625	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	16/11/2015	n/a		
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/06/2015	10/12/2015	PL	
IB/0058	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	26/05/2015	10/12/2015	SmPC	
WS/0688	This was an application for a variation 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	23/04/2015	27/05/2015	Annex II	

	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				
WS/0698/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. Submission of the final report for Vaccine Impact Population study in 4 Nordic countries for P033 and extension of the due date from June 2015 to December 2015 for the submission of final study report MEA 20.6 for Protocol 018 (long-term follow up study in adolescents). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/03/2015	n/a		
IAIN/0057	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	02/03/2015	n/a		
WS/0643	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	18/12/2014	n/a		

	Submission of the final pregnancy registry report in order to address PAMs MEA 065 (Gardasil) and MEA 064 (Silgard) on submission of annual pregnancy registry reports with consequential update of the RMP to version 8. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUV/0052	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
WS/0637	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. As requested by the PRAC and CHMP (LEG 079), Update of section 4.8 of the SmPC to add acute disseminated encephalomyelitis (ADEM) as an adverse reaction. Section 4 of the PL is updated accordingly. Editorial corrections were also made in section 5.1 of the SmPC. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/10/2014	27/05/2015	SmPC and PL	
IB/0054	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/10/2014	n/a		
WS/0545	This was an application for a variation following a worksharing procedure according to Article 20 of	26/06/2014	27/05/2015	SmPC and PL	The long term effectiveness is demonstrated with no cases of HPV disease observed at a median follow-up of 6.8 years

	Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC to include long-term effectiveness, immunogenicity, and safety data of qHPV vaccine. In addition, the MAH took the opportunity to slightly amend the Package Leaflet with the addition of a sentence to correct a discrepancy between vial and pre-filled syringe and to amend the contact details for the Danish contact in the list of representatives (the latter applicable to Gardasil only). Furthermore section 2 of the outer packaging for pre-filled syringes was revised to remove the word "dose" that was repeated (applicable to Gardasil only). The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, labelling and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				post vaccination in preadolescent and adolescent girls and boys and with observed persistent immunogenicity in all HPV types. Few vaccine-related adverse events were reported from the 96 month data of this study in preadolescent and adolescent girls and boys. Data from other long-term follow-up studies covering all the populations studied (including Young Adult Women, Mid-Adult Women and Adult Men) support the long term effectiveness, immunogenicity and safety of the qHPV vaccine.
WS/0523	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of the indication to include prevention of premalignant anal lesions and anal cancer. Consequently sections 4.1, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly.	25/04/2014	06/06/2014	SmPC and PL	Please refer to the CHMP assessment report EMEA/H/C/WS/000703-000732/0523

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0435	A.1 - Administrative change - Change in the name and/or address of the MAH	06/05/2014	06/06/2014	SmPC, Labelling and PL	
IG/0434	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	09/04/2014	n/a		
WS/0472	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	27/03/2014	SmPC, Annex II, Labelling and PL	Please refer to the CHMP assessment report EMEA/H/C/WS/00703-745/0472.
IB/0046	B.II.e.4.z - Change in shape or dimensions of the container or closure (immediate packaging) - Other variation	10/01/2014	n/a		
PSUV/0044	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
WS/0425/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.	19/09/2013	n/a		

	Change to drug product release test method. Change to in-process tests applied during the manufacture of the drug product. 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.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/07/2013	27/03/2014	PL	
IG/0312	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/06/2013	n/a		
IA/0039	A.7 - Administrative change - Deletion of manufacturing sites	30/04/2013	n/a		
WS/0315	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the Summary of Product Characteristics (SmPC) to revise the warning on syncope (fainting) that can be accompained by sevral neurological symptoms as requested by CHMP following the assessment of the Periodic Safety Update Reports 9 and 10. The Package Leaflet was updated accordingly.	18/10/2012	30/11/2012		Cases of loss of vision / blindness, paraesthesia and anxiety have been reported. These reactions can occur in addition to syncope and are likely psychogenic effects associated with the vaccine procedure. Procedures should be in place to avoid injury from faints and comprehensive information should be provided to healthcare professionals and patients The CHMP recommended revising the qHPV vaccine SPC and Package Leaflet to reflect these reactions.

	In addition the MAH took the opportunity to introduce the following administrative changes: a) reflect the renewal date b) correct translation typos in Dutch, German, Finnish and Islandic language. Furthermore, the RMP number was updated. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
WS/0300	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of a manufacturing facility involved in the manufacturing process for Alum. 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.	20/09/2012	n/a		
WS/0241	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a	19/04/2012	22/05/2012	SmPC and PL	Quadrivalent Human Papillomavirus vaccine was given to 126 HIV infected subjects aged 7-12 years in an academic study. Ninety-six percent of the subjects seroconverted, but the GMTs were lower than what has been reported in non-HIV infected subjects of the same age in other studies. The clinical relevance of the lower response is unknown.

	PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				The safety profile was similar to non-HIV infected subjects in other studies. The CD4% or plasma HIV RNA was not affected by vaccination.
WS/0227	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. additional alternative manufacturing facility used in drug substance manufacturing process 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	15/03/2012	15/03/2012		
WS/0211	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of an alternative facility involved in the manufacture of the Bulk Alum Diluent 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	15/03/2012	15/03/2012		
IG/0156	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	24/02/2012	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
WS/0142	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.8 of the SmPC in order to update the safety information [include cellulitis to the list of undesirable effects in section 4.8]. The PL 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	17/11/2011	19/12/2011	SmPC and PL	The cumulative analysis of reports of cellulitis (an inflammatory condition of the skin) among persons vaccinated with qHPV vaccine in clinical trials, from post-marketing spontaneous reports and the information from the observational post-authorisation safety study in females provided supportive evidence that cellulitis may be increased after qHPV vaccination.
WS/0029	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics, Annex II and Package Leaflet To change the indication to genital warts and include P020 study results in section 5.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/06/2011	16/11/2011	SmPC, Annex II and PL	Please refer to Assessment Report WS/29.
R/0029	Renewal of the marketing authorisation.	19/05/2011	27/07/2011	SmPC, Annex II, Labelling	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

				and PL	efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Gardasil continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Gardasil with unlimited validity.
IG/0059/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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	15/04/2011	n/a		
II/0026	Extension of Indication	24/06/2010	18/08/2010	SmPC, Annex II and PL	Please refer to Assessment Report II/26.
II/0025	To update section 4.8 of the SmPC to include the adverse reaction idiopathic thrompocytopenic purpurea (ITP). The PL was updated accordingly. The MAH took the opportunity of this variation to update the PI with the name of the agency and to include the sentence that further information about the product can be found on the Agency website. Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	12/05/2010	SmPC, Annex II and PL	The MAH provided safety information regarding idiopathic thrombocytopenic purpura (ITP) and acute disseminated encephalomyelitis (ADEM) based on routine pharmacovigilance activities that have been conducted since the approval of the vaccine. Cumulative analysis of these adverse events and full description of cases that occurred were assessed. These data were considered sufficient to support the enclosure of the adverse events ITP to section 4.8 of the SPC based on the notion that it may be biologically plausible that non-specific immune

					stimuli, including vaccinations, could precede cases of ITP in susceptible individuals. However, regarding ADEM the additional clarification and information provided did not justify the enclosure in section 4.8 of the SPC as yet. Close monitoring, cumulative reporting and commenting on all such events will continue in future PSURs.
IA/0028/G	This was an application for a group of variations. To change in the name of the Drug substance and drug product manufacturer. Following the merger between Merck & Co., Inc. and Schering-Plough Corporation, the name of the company has changed from Merck & Co., Inc. to Merck Sharp & Dohme Corp. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	18/03/2010	n/a	Annex II	
IB/0027	To tighten specification limits for the active substance B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	17/03/2010	n/a		

II/0024	Update of the detailed description of pharmacovigilance system (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). The version number of the DDPS in Annex II has been updated accordingly. The MAH also took the opportunity to update the version number of the Risk Management Plan in Annex II. Update of DDPS (Pharmacovigilance)	17/12/2009	19/01/2010	Annex II	The DDPS has been updated (version 2.0) to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
II/0020	To update sections 4.2, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SPC based on the results of an efficacy, immunology and safety study in mid-adult women, 24 to 45 years of age. Sections 1, 3 and 4 of the PL were updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to introduce other minor changes to the SPC. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	31/08/2009	SmPC and PL	This will refer to the scientific discussion of this assessment report: Gardasil-H-703-II-20-AR Scientific Discussion
II/0023	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.5 and 4.8 of the SPC to reflect the result from protocol 024 on the concomitant administration of the qHPV vaccine with combined diphtheria, tetanus, pertussis and/or poliomyelitis booster vaccines. Sections 2 and 4 of the PL were updated accordingly. The MAH took the opportunity of this variation to revise section 3 of the PL to better	25/06/2009	24/07/2009	SmPC and PL	The Gardasil development program aimed to assess the concomitant use of Gardasil with other vaccines that might be administered to the same age group. At the time of the marketing authorisation the MAH committed to perform a study to evaluate the safety, tolerability, and immunogenicity of the concomitant administration of the first dose of Gardasil with a diphtheria(d)-tetanus(T)-acellular pertussis(ap)-inactivated poliovirus(IPV) (dTap-IPV) vaccine versus the administration of Gardasil non-concomitantly with dTap-IPV in healthy male and female

	reflect information of the SPC. Update of Summary of Product Characteristics and Package Leaflet				adolescents 11 to 17 years of age. The study is finalised and results show no significant interference with antibody response to any of the components of either vaccine. Gardasil can therefore be given with a combined booster vaccine containing diphtheria and tetanus with either pertussis [acellular, component] and/or poliomyelitis [inactivated] (dTap, dT-IPV, dTap-IPV vaccines) at a separate injection site (another part of your body, e.g. the other arm or leg) during the same visit. The safety data reported between concomitant vaccination group versus non-concomitant vaccination group were generally comparable although injection site swelling and headache were reported at higher frequency in the concomitant group.
II/0022	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 of the SPC to add "chills" as a post-marketing adverse reaction. Section 4 of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	23/04/2009	28/05/2009	SmPC and PL	A cumulative review up to 30 Sep 2008 of adverse drug reactions identified 217 reports of chills. 30 (14 %) of these reports were marked as serious. Although the symptom of chills was most often associated with other adverse reactions such as fever, chills are a distinct symptom. Therefore the product information was revised to add "chills" in order to inform health care professionals and patients of the possibility of the occurrence of this adverse reaction.
II/0021	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 on syncope that sometimes is accompanied by tonic clonic movements. Section 4 of the PL was updated	22/01/2009	04/03/2009	SmPC and PL	The ongoing review and analysis of adverse drug reactions identified nineteen reports with syncope accompanied by tonic-clonic movements. The onset of syncopal episodes and accompanying movements occurred in very close temporal relationship following administration of the vaccine. The duration of the episodes was generally very

	accordingly. Update of Summary of Product Characteristics and Package Leaflet				brief, and there was the absence of other hallmarks of seizures in the descriptions of the events. The description of seizure-like activity found in these reports was typical of tonic clonic movements known to accompany syncopal episodes. The product information was revised to add "syncope sometimes accompanied by tonic-clonic movements" in order to alert health care professionals of the possibility of abnormal movements accompanying syncopal episodes; this information is expected to aid appropriate patient evaluation and care as well as improve accuracy of reporting
II/0019	Update of Summary of Product Characteristics To update sections 4.6, 4.8 and 5.1 of the SPC with end-of-study results of the pivotal clinical studies (P013 and P015). Update of Summary of Product Characteristics	18/12/2008	02/02/2009	SmPC	With the present type II variation application the MAH has updated the SPC with end-of-study (final) results of the pivotal clinical studies of Garadsil, Protocol 013 (Future I) and Protocol 015 (Future II), with efficacy data at ~3.5 years. The end-of-study results confirm and strengthen the efficacy findings in the marketing authorisation application. Vaccine efficacy against the primary endpoint, HPV 16/18-related CIN 2/3 or AIS, remained high and there is no evidence of waning immunity. Efficacy against HPV 6/11/16/18-related genital warts (condyloma acuminata) remained high in all study populations. The analysis of public health impact revealed a noticeable reduction in the overall burden of CIN 2/3 or AIS in the HPV-naïve population whereas the impact on the general population was limited. As regards population benefit, clinically relevant reductions in the incidence of colposcopy,

					cervical biopsy and definitive therapy procedures were observed in the vaccine group in the HPV-naïve population, and in the general population. There was no evidence of therapeutic vaccine efficacy in subjects with evidence of infection/disease at the time of vaccination. The analysed safety report did not include any new or unexpected reports of adverse experiences.
II/0018	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 of the SPC and section 4 of the PL with the adverse events reported in the third PSUR, which are arthralgia, myalgia, asthenia, fatigue and malaise. In addition, the MAH takes the opportunity to add the warning regarding possible syncope following vaccination in section 4.4 "Special warnings and precaution for use" of the SPC. Furthermore the contact details of the local representative in Denmark were updated in the PL. Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	31/10/2008	SmPC and PL	Following a cumulative review of the New Worldwide Adverse Event System database performed by the MAH for the period from market introduction to 28-Sep-2007 including spontaneous reports with Silgard the MAH identified the following adverse reactions arthralgia, myalgia, asthenia, fatigue and malaise. These reactions were added to the heading postmarketing experience of section 4.8 of the SPC.
II/0006	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.4 and 5.1 on efficacy data on cross-protection persistent infection from protocol 012 and on disease cross-protection from combined	26/06/2008	02/09/2008	SmPC and PL	This will refer to the scientific discussion of this assessment report: Gardasil-H-703-II-06-AR Scientific Discussion

	protocols 013 and 015. The PL was updated with minor linguistic changes. Update of Summary of Product Characteristics and Package Leaflet				
II/0013	Extension of Therapeutic Indication to include the prevention of high-grade vaginal dysplastic lesions (VaIN 2/3) Extension of Indication	30/05/2008	10/07/2008	SmPC and PL	This will refer to the scientific discussion of this assessment report: Gardasil-H-703-II-13-AR Scientific Discussion
II/0016	Update of or change(s) to the pharmaceutical documentation	30/05/2008	11/06/2008		
II/0015	Change(s) to the manufacturing process for the active substance	19/03/2008	28/03/2008		
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/02/2008	n/a	PL	
IB/0014	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	03/10/2007	n/a		
II/0007	Change(s) to the manufacturing process for the finished product	20/09/2007	27/09/2007		
IA/0012	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/08/2007	16/08/2007	SmPC, Labelling and PL	
IA/0011	IA_41_a_01_Change in pack size - change in no. of	16/08/2007	16/08/2007	SmPC,	

	units within range of appr. pack size			Labelling and PL	
IA/0010	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/08/2007	16/08/2007	SmPC, Labelling and PL	
IA/0009	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/08/2007	16/08/2007	SmPC, Labelling and PL	
II/0005	To update section 4.8 of SPC on post-marketing experience following spontaneous reports of adverse reactions. Section 4 of the PL was updated accordingly. The MAH took the opportunity of this variation to split the PL for the prefilled syringe in one PL for the prefilled syringe with safety device and one PL for the prefilled syringe without safety device. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	Following the submission of the first PSUR for Gardasil (covering the period 1 June 2006 to 30 November 2006) and further spontaneous adverse reactions reports the following adverse reactions were identified to be introduced in the product information: syncope, dizziness, nausea, vomiting and hypersensitivity reactions including anaphylactic/anaphylactoid reactions.
II/0003	To update section 6.6 of the SPC and section 6 of the PL for the pre-filled syringes to improve the instructions for use of the syringes with the needle guard safety device. Furthermore, the MAH took the oportunity of this change to introduce the MA numbers, the date of the first authorisation and to perform minor changes in the PI (for pre-filled syringes and vials). Update of Summary of Product Characteristics and	26/04/2007	13/06/2007	SmPC and PL	The MAH has revised the SPC and PL to improve the instructions for use of the pre-filled syringes with the needle guard safety device. This revision was based on the results of a user test for healthcare professionals and included stepwise illustrations, clarification/simplification of terms and adding missing information.

	Package Leaflet				
II/0004	Change(s) to the manufacturing process for the finished product	24/05/2007	06/06/2007		
II/0001	Change(s) to the manufacturing process for the active substance	22/03/2007	30/03/2007		
N/0002	The MAH completed the list of local representatives in the PL to inlcude the two new EU Member States (Bulgaria and Romania) according to the latest EMEA/QRD template. Furthermore minor gramatical and thypographical error were corrected as well as an update of the local representatives in Ireland and Finland. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/01/2007	n/a	Labelling and PL	