Ambirix

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/2594/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.7 - Administrative change - Deletion of	01/02/2024		Annex II	

[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).

	manufacturing sites B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
WS/2470/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.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	31/08/2023	n/a		
IG/1651/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved	22/08/2023	n/a		

	manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
WS/2476	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	06/07/2023	n/a		
WS/2445	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.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	15/06/2023	n/a		
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 an integrated part of the primary packaging	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. 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.
WS/2443	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	23/03/2023	n/a		
WS/2333	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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/11/2022	n/a		
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		
WS/2291/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.	08/09/2022	n/a		

	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability 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 B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a				

	safety or quality issue				
WS/2231	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 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	19/05/2022	n/a		
PSUSA/1593/ 202109	Periodic Safety Update EU Single assessment - hepatitis A (inactivated) / hepatitis B (rDNA) vaccines (adsorbed)	05/05/2022	n/a		PRAC Recommendation - maintenance
WS/2155	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/01/2022	03/02/2023	SmPC, Annex II and PL	
IG/1449	A.7 - Administrative change - Deletion of manufacturing sites	09/11/2021	n/a		
IG/1441	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	05/10/2021	n/a		

WS/2076	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	22/07/2021	n/a		
WS/2042	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)	10/06/2021	n/a		
WS/2018/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.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	20/05/2021	n/a		

WS/1994	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	11/03/2021	n/a		
WS/1988	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)	11/03/2021	n/a		
WS/1912	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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/11/2020	n/a		
WS/1878	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	26/11/2020	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
WS/1902/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.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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 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 B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	22/10/2020	n/a		
WS/1826	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.III.1.b.5 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New/updated certificate from an already approved/new manufacturer using materials of	23/07/2020	n/a		

	human/animal origin for which a risk assessment on potential contamination with adventitious agents is required				
IG/1250	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	16/06/2020	n/a		
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 procedure is already authorised	14/05/2020	n/a		
II/0105	Update of sections 4.2 and 5.1 of the Ambirix SmPC in order to reflect information on the long-term antibody persistence and immune memory up to 15 years after primary immunisation of adolescents, based on data from the Phase IV study HAB-084 EXT Y11-15 (An open, long-term follow-up study to evaluate long-term antibody persistence and immune memory between 11 and 15 years after the primary study HAB-084). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1.	26/03/2020	22/03/2021	SmPC, Annex II and PL	The results obtained from a long-term follow-up extension study conducted in healthy adolescents of 12-15 years, tested 15 years after the primary vaccination with Ambirix, showed anti-HAV seropositivity rates of 100% and anti-HBs seroprotection rates of 81.1%. These data show the long-term persistence of immune memory for both hepatitis A and B vaccination with Ambirix, suggesting a sustained long term protection.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1720/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.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 biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes 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	27/02/2020	n/a		
WS/1670	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.z - Quality change - Finished product - Other variation	25/07/2019	n/a		
IG/1121	A.7 - Administrative change - Deletion of manufacturing sites	16/07/2019	n/a		

WS/1593	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.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	11/07/2019	n/a		
IG/1097	A.7 - Administrative change - Deletion of manufacturing sites	18/06/2019	n/a		
IG/1096	A.7 - Administrative change - Deletion of manufacturing sites	29/05/2019	n/a		
IG/1095	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	29/05/2019	n/a		
WS/1567	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 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	16/05/2019	n/a		
PSUSA/1593/	Periodic Safety Update EU Single assessment -	16/05/2019	n/a		PRAC Recommendation - maintenance

201809	hepatitis A (inactivated) / hepatitis B (rDNA) vaccines (adsorbed)				
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		
WS/1432	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.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	14/03/2019	n/a		
IG/1063/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its	31/01/2019	n/a		

	corresponding test method B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method				
WS/1420	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 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	17/01/2019	n/a		
WS/1365/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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall	05/07/2018	n/a		

	quality of the AS				
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		
WS/1237/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.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	22/02/2018	n/a		
WS/1240/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.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved	09/11/2017	n/a		

	manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.z - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Ph. Eur. TSE Certificate of suitability - Other variation				
WS/1223	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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/11/2017	n/a		
N/0088	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2017	22/03/2021	Labelling	
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 material/intermediate/reagent - Where there is no	05/10/2017	n/a		

	monograph in the European/National Ph. for the AS, a change in specification from in-house to a non-official/third country Ph.				
WS/1115/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.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	18/05/2017	n/a		
WS/1046	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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/02/2017	n/a		

IG/0738	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	16/12/2016	n/a		
WS/1007	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	15/12/2016	n/a		
II/0077	Update of section 6.6 of the SmPC in order to improve the re-suspension instructions following receipt of customers' complaints with regards to unusual vaccine appearance and based on user testing results. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1, to include some corrections and to align the wording across combined hepatitis A and hepatitis B vaccines (i.e. Twinrix Adult, Twinrix Paediatric and Ambirix). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	09/10/2017	SmPC, Labelling and PL	Following receipt of customers' complaints with regards to 'unusual vaccine appearance' for hepatitis A and B vaccines often described as 'cloudy vaccine' or 'particles in vaccine', the MAH initiated an investigation into these complaints. The aluminium salt used as adjuvant can settle during storage and form an insoluble pellet which can break into particles if not sufficiently re-suspended prior to administration of the vaccine. The MAH therefore proposed to improve the re-suspension instructions intended for health care professionals, based on the results of a user testing, in order to obtain a uniform hazy white suspension prior to administration.

IG/0721	A.7 - Administrative change - Deletion of manufacturing sites	10/10/2016	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		
IG/0682	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	19/05/2016	n/a		

PSUSA/1593/201509	Periodic Safety Update EU Single assessment - hepatitis A (inactivated) / hepatitis B (rDNA) vaccines (adsorbed)	14/04/2016	n/a		PRAC Recommendation - maintenance
WS/0812	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	04/02/2016	n/a		
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/11/2015	09/10/2017	PL	
IG/0540	A.7 - Administrative change - Deletion of manufacturing sites	26/06/2015	n/a		
WS/0728	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	25/06/2015	n/a		
PSUSA/1593/201409	Periodic Safety Update EU Single assessment - hepatitis A (inactivated) / hepatitis B (rDNA) vaccines (adsorbed)	10/04/2015	n/a		PRAC Recommendation - maintenance

WS/0612/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.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 B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	22/01/2015	n/a		
WS/0610/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.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	22/01/2015	n/a		
IG/0499	A.7 - Administrative change - Deletion of	05/12/2014	n/a		

	manufacturing sites				
WS/0603	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.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	20/11/2014	n/a		
WS/0591	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	20/11/2014	n/a		
WS/0593	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.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	23/10/2014	n/a		

WS/0592	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This was an application following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	23/10/2014	n/a		
II/0062	Update of section 5.1 of Ambirix SmPC with new assay (CLIA) data for the persistence of the anti-HBs antibody response ten years after primary vaccination. Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 9.0. Finally, minor editorial amendments are made throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	08/07/2015	SmPC, Annex II, Labelling and PL	Although the results of the retesting with the anti-HBs CLIA showed that the percentage of subjects having an anti-HBs antibody concentration > 10mIU/ml tends to be lower than with the initial ELISA test (77.3% versus 81.7%), this 4.4% difference observed at Year 10 post-primary vaccination is considered unlikely to be of clinical relevance, as an anamnestic response was obtained in all subjects following a challenge dose. The persistence of antibody 10 years after the primary vaccination is still demonstrated for the majority of subjects and the immunogenicity profile is considered unchanged.
WS/0551	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.a - Change in test procedure for the finished product - Minor changes to an approved test	26/06/2014	n/a		

	procedure				
WS/0515	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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/06/2014	n/a		
WS/0553	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)	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		
WS/0505/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.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch	22/05/2014	n/a		

	release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs				
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 - Minor changes to an approved test procedure	25/04/2014	n/a		
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		
PSUV/0055	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
WS/0445/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.	20/03/2014	n/a		

	-Additional manufacturer of finished product. -Additional quality control testing manufacturer of the product. -Scale up of active substance of vaccine. -Introduction of alternative containers for the active substance. 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 biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes 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 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) B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs				
WS/0415	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	23/01/2014	n/a		

	Change in specifications of active substance. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS				
WS/0439/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. Change in the specification parameters of a raw material . B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	18/12/2013	n/a		
N/0053	Minor change in labelling or package leaflet not	12/12/2013	08/07/2015	PL	

	connected with the SPC (Art. 61.3 Notification)				
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		
IG/0329	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	30/08/2013	n/a		
IG/0306	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2013	n/a		
IG/0299	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	26/04/2013	n/a		
IG/0297	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2013	n/a		
II/0044	Replacement of the current screw caps used for the purified bulk transfer and storage. B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for	21/02/2013	n/a		

	sterile and non-frozen biological/immunological ASs				
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		
R/0042	Renewal of the marketing authorisation.	24/05/2012	20/07/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considered by consensus that the risk-benefit balance of Ambirix in non-immune children and adolescents from 1 year up to and including 15 years for protection against hepatitis A and hepatitis B infection, remains favourable and therefore recommends the renewal of the marketing authorisation with unlimited validity. Based on the available safety information regarding the large proportions of administration errors due to confusion between Hepatitis A/Hepatitis B combination vaccines, the CHMP also considered that the MAH should continue to provide yearly PSUR.
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				
II/0034	Update of section 4.8 of the SmPC in order to include immediate injection site pain, stinging and burning sensation. The PL is updated in accordance. In addition, the MAH took the opportunity to make minor corrections to the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/12/2011	06/02/2012	SmPC and PL	Following clusters of spontaneous reports of immediate onset injection site pain reported in certain batches of the preservative-free formulation of Twinrix Adult and Twinrix Paediatric, 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 for other combined or monovalent hepatitis A and hepatitis B vaccines. 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. It is acknowledged that similar clusters of cases have not been reported for Ambirix. However, considering that the product's formulation is the same as Twinrix Adult, section 4.8 of the SmPC and section 4 of the package leaflet for Ambirix have been updated. The benefit-risk of Ambirix remains positive.
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.	19/01/2012	n/a		

	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 procedure				
WS/0153	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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 4.4 of the SmPC to include a warning on psychogenic syncope based on the available safety data. The PL was proposed to be updated in accordance. In addition, the company took the opportunity to update the list of local representatives in the PL of Pumarix, Ambirix,	17/11/2011	22/12/2011	SmPC and PL	Based on a review of literature and a search in the global safety database performed by the MAH, the CHMP recommended including a wording on psychogenic syncope to the product information of the MAH injectable vaccines. The literature review showed an incidence peak occurred around the age of 15 years, with females having more than twice the incidence of males. The syncope reports with secondary injuries were reported most frequently in children and adolescents. Given that psychogenic syncope is not a true side effect, it was not considered appropriate to include syncope as an undesirable effect in section 4.8 of the SmPC. However, as such events can result in injury, and may not have

	Pandemrix, Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals, Prepandrix and Fendrix. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				occurred in the absence of the vaccination, the CHMP recommended to add a reference to such events in section 4.4 'Warning and Precaution' of the SmPC and in the PL.
IB/0033	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/12/2011	n/a		
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		
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	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

	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 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				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.
WS/0001	This was an application for a variation following a	22/04/2010	22/04/2011		

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To register an additional building for formulation activities. 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.				
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 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)	18/03/2011	n/a		
II/0031	Registration of a new Hepatitis A working seed. B.I.a.2.c - Changes in the manufacturing process of	16/12/2010	04/01/2011		

	the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol				
II/0029	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/10/2010	26/11/2010	SmPC and PL	Based on a review of post marketing surveillance (PMS) data, the Product Information was updated to include adverse event terms from a cumulative review of Ambirix PMS data (Syncope, Anaphylaxis/allergic reactions, localised Hypoaesthesia) and adverse event terms previously included in the Twinrix Adult SmPC (Angioneurotic oedema, Paralysis, Neuritis, Neuropathy, Lichen planus, Arthritis, Muscular weakness). In addition, this variation also updated section 4.9 of the Ambirix SmPC to harmonise the information on overdose with that of the Twinrix Adult SmPC to remove wording referring to thiomersal containing formulations from sections 4.8 and 5.1 of the Ambirix SmPC to harmonise with the SmPCs for Fendrix and Twinrix. The MAH made also minor changes to wording and format to comply with the updated Guideline on SmPC, as well as the QRD template.
II/0032	Update of Summary of Product Characteristics and Package Leaflet. To update section 4.2 "Posology and method of administration" and section 5.1 "Pharmacodynamic properties" of the SmPC with data from four long-term immune persistence studies: HAB-137 and HAB-152 which were conducted in children 1 to 11 years old and HAB-159 and HAB-157 which were conducted in adolescents 12 to 15 years old.	23/09/2010	28/10/2010	SmPC and PL	

	In addition, the MAH took the opportunity to update the PL to reflect that recommendations should be addressed not only to children/adolescents but also to their adult guardians. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0030	To update the internal monograph for a raw material used in the manufacure of the active substance. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	23/09/2010	29/09/2010		
II/0028	Change in cell identity method. Change to the test procedure and/or specification of a raw material	17/12/2009	06/01/2010		
II/0027	Changes to the raw materials used in the manufacturing process of the Hepatitis A Viruses (HAV) antigens. Change to the test procedure and/or specification of a raw material	19/11/2009	25/11/2009		
IB/0026	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	18/09/2009	n/a		

IB/0025	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	20/07/2009	n/a		
II/0023	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	02/07/2009		
IB/0024	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	19/06/2009	n/a		
IA/0022	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/02/2009	n/a		
IA/0021	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/07/2008	n/a		
IA/0020	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	07/05/2008	n/a		
IA/0019	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	07/12/2007	n/a		
R/0018	Renewal of the marketing authorisation.	21/06/2007	07/09/2007	SmPC, Annex II, Labelling and PL	
II/0015	Change(s) to the manufacturing process for the active substance	16/11/2006	03/01/2007	SmPC, Annex II, Labelling and PL	

II/0017	Change(s) to the manufacturing process for the finished product	16/11/2006	27/11/2006		
II/0012	Change(s) to the manufacturing process for the active substance	27/04/2006	03/05/2006		
II/0013	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	15/09/2005	26/09/2005		
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2005	n/a	Labelling and PL	
II/0010	Extension of Indication Update of Summary of Product Characteristics and Package Leaflet	21/01/2004	31/03/2004	SmPC, Labelling and PL	
IA/0011	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/03/2004	n/a		
II/0007	Quality changes	22/10/2003	30/10/2003		
II/0006	Quality changes	22/10/2003	30/10/2003		
II/0005	Change(s) to the test method(s) and/or specifications for the finished product	25/09/2003	02/10/2003		
I/0009	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	18/07/2003	23/07/2003		

II/0004	Change(s) to the manufacturing process for the active substance	20/02/2003	06/03/2003		
II/0003	Change(s) to shelf-life or storage conditions	19/12/2002	09/01/2003		The scientific data provided in support of this variation, was considered satisfactory as per the annexed Rapporteur's variation Assessment Report, therefore the variation is considered acceptable.
II/0002	Quality changes	18/12/2002	09/01/2003		The scientific data provided in support of this variation, was considered satisfactory as per the annexed Rapporteur's variation Assessment Report, therefore the variation is considered acceptable.
II/0001	Change(s) to the test method(s) and/or specifications for the active substance	19/12/2002	09/01/2003		The scientific data provided in support of this variation, was considered satisfactory as per the annexed Rapporteur's variation Assessment Report, therefore the variation is considered acceptable.