Twinrix Adult

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	12/01/2023	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/0140	Update of sections 4.2 and 5.1 of the Twinrix Adult SmPC in order to reflect information on the long-term antibody persistence and immune memory up to 20 years after primary immunisation of adults, based on data from two phase IV long-term follow-up extension studies, HAB-028 EXT Y16-20 (An open, single centre study to evaluate the long-term antibody persistence and immune memory between 16 and 20 years after the primary study HAB-028) and HAB-032 EXT Y16-20 (An open single centre study to evaluate the long-term antibody persistence and immune memory between 16 and 20 years after	26/03/2020	10/03/2021	SmPC and Annex II	The results obtained from two long-term follow-up extensions studies conducted in adults aged 17 years to 43 years, tested 20 years after the primary vaccination with Twinrix Adult, showed anti-HAV seropositivity rates of 100% and 96%, and anti-HBs seroprotection rates of 94% and 92%. These data show the long-term persistence of immune memory for both hepatitis A and B vaccination with Twinrix Adult, suggesting a sustained long term protection.

	the primary study HAB-032). In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1. 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	25/07/2019	n/a		

	variation				
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	16/05/2019	n/a		

	which may have a significant impact on the medicinal product and is not related to a protocol				
PSUSA/1593/ 201809	Periodic Safety Update EU Single assessment - hepatitis A (inactivated) / hepatitis B (rDNA) vaccines (adsorbed)	16/05/2019	n/a		PRAC Recommendation - maintenance
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	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 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		
IG/0960	B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	24/09/2018	13/09/2019	SmPC, Annex II, Labelling and PL	
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.	05/07/2018	n/a		

	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 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	22/02/2018	n/a		

	(including replacement or addition)				
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 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	09/11/2017	n/a		
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/0122	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2017	13/09/2019	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 monograph in the European/National Ph. for the AS, a change in specification from in-house to a non-official/third country Ph.	05/10/2017	n/a		
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	18/05/2017	n/a		

	material/intermediate/reagent - Other variation				
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/0110	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	10/11/2016	04/10/2017	SmPC, Annex II, 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

	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				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	21/09/2016	n/a		

	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				
IG/0679	B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	01/06/2016	n/a		
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/0108	Minor change in labelling or package leaflet not	12/11/2015	02/12/2015	PL	

	connected with the SPC (Art. 61.3 Notification)				
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		
IB/0103	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/01/2015	02/12/2015	SmPC, Annex II, Labelling and PL	
IG/0499	A.7 - Administrative change - Deletion of manufacturing sites	05/12/2014	n/a		
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.	20/11/2014	n/a		

	Submission of final study report of a post-approval clinical study to compare the current and the new plunger stoppers and tip caps in response to a CHMP recommendation. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
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		

IG/0467	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	20/08/2014	n/a		
WS/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 procedure	26/06/2014	n/a		
WS/0515	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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 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	22/05/2014	n/a		
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.	25/04/2014	n/a		

	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				
PSUV/0087	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. -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	20/03/2014	n/a		

	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. 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	23/01/2014	n/a		
N/0084	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/01/2014	02/12/2015	PL	
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 .	18/12/2013	n/a		

	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)				
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/0076	Replacement of the current screwcaps 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 sterile and non-frozen biological/immunological ASs	21/02/2013	n/a		
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		
WS/0239	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 site for QC sterility	19/04/2012	n/a		

	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				
IG/0160	A.7 - Administrative change - Deletion of manufacturing sites	09/03/2012	n/a		
WS/0201/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To propose new target fill volume controls. To align the volume specifications to be applied at release and during stability evaluation. To revise QC release procedures for final container volume determination. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	19/01/2012	n/a		

	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, 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	17/11/2011	13/01/2012	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 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.
II/0064	Update of section 4.8 of the SmPC to include immediate injection site pain, stinging and burning sensation. The PL is updated in accordance. The MAH has also taken the opportunity to align section 4.6 of the prefilled syringe presentation with the vial presentation. Furthermore, the Labelling is updated	17/11/2011	13/01/2012	SmPC, Labelling 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, immediate pain, stinging and burning at the injection site has been reflected in section 4.8 of the SmPC and section 4 of the package leaflet. The MAH's investigation report revealed no

	to specify the container 'prefilled syringe'. In addition, the MAH has taken the opportunity to update the list of local representatives in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				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.
IB/0065	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		
II/0063	To update sections 4.2 and 5.1 of the SmPC with data from two long-term immune persistence studies in adults. In addition, minor changes are made in section 4.6 according to the QRD template and in section 6.6 for consistency with other hepatitis	19/05/2011	23/06/2011	SmPC and PL	The MAH has provided the long-term results of two follow-up studies conducted in adults aged 17 years to 43 years. The objective of these studies was to evaluate anti-HAV and anti-HBs antibody persistence at years 11, 12, 13, 14 and 15 after the first vaccine dose of three-dose primary

	vaccines. The MAH has also taken the opportunity to include minor changes in the package leaflet (EMA acronym, information intended for medical and healthcare professionals in line with SmPC). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				vaccination. In addition, the immune memory in subjects who became seronegative for anti-HAV antibodies (i.e. concentrations < 15 mIU/ml) or had anti-HBs antibody concentrations < 10 mIU/ml at the long-term blood sampling time-point (years 11, 12, 13, 14 or 15) and who received an additional dose of Engerix-B, was also evaluated. 56 subjects had evaluable tests 15 years after the primary vaccination with Twinrix Adult. The anti-HAV seropositivity rates were 100% in both studies and the anti-HBs seroprotection rates were 89.3% and 92.9%, respectively. The data obtained also suggest that in the few subjects who respond to primary vaccination but loose seroprotection level of hepatitis B antibodies, protection could still be conferred through immune memory. The SmPC has been revised to reflect this information.
IG/0064/G	This was an application for a group of variations. Update of section 4.8 of the SmPC to include immediate injection site pain, stinging and burning sensation. The PL is updated in accordance. The MAH has also taken the opportunity to align section 4.6 of the prefilled syringe presentation with the vial presentation. Furthermore, the Labelling is updated to specify the container 'prefilled syringe'. In addition, the MAH has taken the opportunity to update the list of local representatives in the PL. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters	04/05/2011	n/a		Following clusters of spontaneous reports of immediate onset injection site pain reported in certain batches of the preservative-free formulation of Twinrix Adult, immediate pain, stinging and burning at the injection site has been reflected in section 4.8 of the SmPC and section 4 of the package leaflet. The MAH's investigation report revealed no specific root cause for the clusters of reports of immediate injection site pain. The injection site reactions were non-serious and self-limited in all cases. The benefit-risk of Twinrix Adult remains positive.

	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				
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	18/03/2011	n/a		

	finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0062	Registration of a new Hepatitis A working seed. 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 medicinal product and is not related to a protocol	16/12/2010	04/01/2011		
II/0061	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	04/10/2010		
WS/0001	This was an application for a variation following a 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.	22/04/2010	22/04/2010		

II/0060	Update of section 5.1 of the SmPC with seroprotection data from two vaccination follow-up clinical studies. In addition, sections 4.8 and 5.1 of the SmPC were amended to delete a wording on thiomersal-containing formulations. The MAH also took the opportunity to update the local list of representatives of the Package Leaflet for Bulgaria, Cyprus and Denmark. Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	15/03/2010	SmPC and PL	Study HAB-163 and study HAB-168 are a 36 month and 48 month respectively long-term follow-up of study HAB-160, previously submitted within variation II/50. Study HAB-163 is a phase IV, open, randomised, multicentre study to evaluate the effect of risk factors likely to influence immunogenicity of combined hepatitis A and B vaccine (Twinrix) according to a 0, 1 and 6 months compared to separately administered monovalent hepatitis A and B vaccines and to demonstrate non-inferiority of Twinrix to the monovalent vaccines, in healthy and non-healthy adults aged 41 years or older. Study HAB-168 evaluated the immune response to a challenge dose of Twinrix versus monovalent hepatitis A and B vaccines 48 months in the same population after primary vaccination from study HAB-160. The SmPC has been updated to add persistence data up to 48 months. In addition, the data on the immune memory response following an additional dose administered at approximately 48 months has been included. In addition, as requested following the assessment and approval of a variation for Fendrix submitted in July 2008 (procedure EMEA/H/C/550/II/0007), that the wording in sections 4.8 and 5.1 of the SmPC for Twinrix Adult, referring to thiomersal containing formulations was removed.
II/0059	Change in cell identity method. Change to the test procedure and/or specification of a raw material	17/12/2009	07/01/2010		

II/0058	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	26/11/2009		
IB/0057	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	18/09/2009	n/a		
IB/0056	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	20/07/2009	n/a		
II/0054	Change to the primary pack stopper and tip cap for pre-filled syringes. Change(s) to the manufacturing process for the finished product	25/06/2009	06/07/2009		
IB/0055	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	19/06/2009	n/a		
IA/0053	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/02/2009	n/a		
IA/0052	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	30/06/2008	n/a		
II/0050	Update of Summary of Product Characteristics and Package Leaflet.	24/04/2008	19/06/2008	SmPC and PL	The effect of risk factors likely to influence the immunogenicity of Twinrix Adult in adults aged 41 years or

	Update of section 4.4 of the SPC with information on the effect of obesity on the immune response to hepatitis A vaccination. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				older was evaluated in an open, randomised, multi-centre and multi-country study in which Twinrix Adult was compared to separately administered monovalent hepatitis A and hepatitis B vaccines. The analysis of anti-HAV seropositivity rates up to 24 months after the first vaccine dose showed that the anti-HAV antibody response was influenced the most by body mass index (BMI), followed by age, gender and the vaccine received. Obese subjects (BMI > 30 kg/m2) achieved significantly lower anti-HAV seropositivity rates compared to subjects with BMI < 30 kg/m2. Based on these findings, the detrimental effect of obesity on the immune response to hepatitis A vaccines has been mentioned in the SPC and PL.
II/0048	Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of section 4.6 of the SPC based on the results from a pre-clinical study and following the review of available clinical data on exposed pregnancies. Section 5.3 was consequentially updated. The MAH also took the opportunity to update section 16 of the Labelling in line with the EMEA/QRD template version 7.2 and to amend the contact details of a local representative in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	19/06/2008	SmPC, Labelling and PL	In a nonclinical study in rats, Twinrix was not associated with any adverse effects on embryo-fetal, pre-natal and post-natal development. There were no findings of toxicity on the parental females or on reproduction. Likewise, no safety concern has been identified based on the limited clinical and post-marketing data of pregnant women exposed to vaccination with Twinrix. However, these limited data should be interpreted with caution and it is recommended that vaccination should be delayed until after delivery unless there is an urgent need to protect the mother against hepatitis B infection.
IA/0051	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	07/05/2008	n/a		

II/0047	Update of Summary of Product Characteristics and Package Leaflet. Update of sections 4.4, 4.8 and 4.9 of the SPC to reflect the safety information obtained through a review of relevant clinical studies and post-marketing surveillance. These changes address the requests made by the CHMP following the assessment of the renewal of Twinrix Adult in June 2006 as well as PSUR 12 (covering the period from 20 September 2005 to 19 September 2006). Section 4 of the PL has been updated accordingly. The MAH also took the opportunity to update the contact details for the local representatives of Romania and Slovakia in the PL and to make minor changes in the SPC in line with the EMEA/QRD template version 7.2 Update of Summary of Product Characteristics and Package Leaflet	13/12/2007	17/01/2008	SmPC and PL	Based on an analysis of pooled safety data from 24 clinical trials and of post-marketing surveillance data, the information on adverse events reported with Twinrix has been comprehensively updated as appropriate. Among these changes, 'hypoaesthesia' (loss of skin sensitivity), 'lichen planus' (bumps on the skin) or 'muscle weakness' have been added to the list of undesirable effects. 'Syncope' has been removed from the list of adverse events since it is attributed to the injection rather than to the vaccine itself, but an appropriate warning was added in section 4.4 of the SPC. The frequency of some adverse events has also been updated. As an example, the frequency of 'headache' has changed from 'common' (occurring in up to 1 in 10 vaccine doses) to 'very common' (occurring in 1 in 10 doses or more). The distinction has also been made clearer in the SPC between the adverse events reported during clinical trials and those reported through post-marketing surveillance. Ten cases of overdose have been reported during post-marketing surveillance. However the adverse events reported following overdosage were similar to those reported with normal vaccine administration.
IA/0049	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	07/12/2007	n/a		
II/0046	Update of Summary of Product Characteristics	21/06/2007	24/07/2007	SmPC	
II/0044	Change(s) to the manufacturing process for the active substance	16/11/2006	04/01/2007	SmPC, Labelling and PL	

II/0045	Change(s) to the manufacturing process for the finished product	16/11/2006	22/11/2006		
R/0043	Renewal of the marketing authorisation.	28/06/2006	28/08/2006	SmPC, Annex II, Labelling and PL	
II/0039	Change(s) to the manufacturing process for the active substance	27/04/2006	03/05/2006		
II/0040	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	03/10/2005		
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2005	n/a	PL	
IA/0041	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	01/08/2005	n/a		
N/0038	To include the local representatives of the ten new EU Member States in the Package Leaflet (PL) and to amend the wording regarding storage conditions in line with the QRD template in the PL and in the labelling. Furthermore minor changes have been made in the following language versions: German, Spanish, Icelandic, Lithuanian, Dutch, Norwegian, Portuguese and Swedish. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/08/2004	n/a	PL	

IA/0037	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/03/2004	n/a		
II/0036	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	30/01/2004	SmPC and PL	
II/0033	Quality changes	22/10/2003	27/10/2003		
II/0032	Quality changes	22/10/2003	27/10/2003		
II/0031	Change(s) to the test method(s) and/or specifications for the finished product	25/09/2003	03/10/2003		
I/0035	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	18/07/2003	23/07/2003		
II/0030	Change(s) to the test method(s) and/or specifications for the active substance	20/02/2003	07/03/2003		
II/0026	Update of Summary of Product Characteristics and Package Leaflet	27/06/2002	24/10/2002	PL	
I/0029	31_Change in container shape	20/09/2002	27/09/2002		
II/0028	Change(s) to shelf-life or storage conditions	25/07/2002	02/09/2002		
II/0027	Quality changes	25/07/2002	02/09/2002		
II/0024	Update of Summary of Product Characteristics	17/01/2002	11/04/2002	SmPC	

II/0025	Change(s) to the test method(s) and/or specifications for the finished product	21/03/2002	03/04/2002		
I/0022	03_Change in the name and/or address of the marketing authorisation holder 01_Change following modification(s) of the manufacturing authorisation(s)	16/11/2001	17/12/2001	SmPC, Annex II, Labelling and PL	
I/0023	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	28/11/2001		
I/0021	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	28/11/2001		
R/0020	Renewal of the marketing authorisation.	26/07/2001	09/11/2001	SmPC, Annex II, Labelling and PL	
II/0018	Update of or change(s) to the pharmaceutical documentation	20/09/2001	20/10/2001		
II/0019	Update of Summary of Product Characteristics and Package Leaflet	26/04/2001	30/08/2001	SmPC and PL	
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/03/2001	17/05/2001	Labelling	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	19/10/2000	20/03/2001	SmPC and PL	
II/0016	Quality changes	14/12/2000	30/01/2001		

I/0014	12_Minor change of manufacturing process of the active substance	21/09/2000	n/a		
II/0013	Change(s) to the test method(s) and/or specifications for the active substance	29/06/2000	29/06/2000		
I/0012	01_Change following modification(s) of the manufacturing authorisation(s)	31/05/2000	29/05/2000		
I/0011	12_Minor change of manufacturing process of the active substance	29/07/1999	14/09/1999		
I/0010	13_Batch size of active substance	29/07/1999	14/09/1999		
I/0009	31_Change in container shape	24/06/1999	09/07/1999		
I/0008	25_Change in test procedures of the medicinal product	25/03/1999	18/05/1999		
I/0007	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	25/03/1999	18/05/1999		
I/0005	20_Extension of shelf-life as foreseen at time of authorisation	06/11/1997	26/01/1999	SmPC	
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/12/1998	14/01/1999	PL	
II/0002	Change(s) to container	23/07/1997	17/11/1997	PL	
I/0004	01_Change following modification(s) of the	31/10/1997	n/a		

	manufacturing authorisation(s)				
I/0003	14_Change in specifications of active substance	24/09/1997	n/a		
I/0001	15_Minor changes in manufacture of the medicinal product	23/07/1997	n/a		