



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## Twinrix Paediatric

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification <sup>1</sup> issued on	Commission Decision Issued <sup>2</sup> / amended on	Product Information affected <sup>3</sup>	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	

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



	<p>manufacturing sites</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p>				
WS/2470/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)</p> <p>B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)</p> <p>B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)</p> <p>B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)</p> <p>B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)</p>	31/08/2023	n/a		
IG/1651/G	<p>This was an application for a group of variations.</p> <p>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</p>	22/08/2023	n/a		

	<p>manufacturer</p> <p>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</p>				
WS/2476	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation</p>	06/07/2023	n/a		
WS/2445	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation</p>	15/06/2023	n/a		
WS/2365	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	26/04/2023		SmPC, Annex II, Labelling and PL	<p>The SmPC Section 4.4 (Bexsero), 6.5 and 6.6 has been updated as follows:</p> <p>Deletion of statement concerning the presence of natural rubber, revision of details for prefilled syringe. Editorial amendments have also been included.</p> <p>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,</p>

					<p>Avenue Fleming 20, 1300 Wavre, Belgium.</p> <p>The Patient Leaflet has been updated accordingly.</p>
WS/2443	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation</p>	23/03/2023	n/a		
WS/2333	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p>	24/11/2022	n/a		
WS/2325	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p>	17/11/2022	n/a		
WS/2291/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p>	08/09/2022	n/a		

	<p>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</p> <p>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</p> <p>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</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>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</p> <p>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)</p> <p>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)</p> <p>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</p>				
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	safety or quality issue				
WS/2231	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p>	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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation</p>	22/07/2021	n/a		
WS/2042	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p>	10/06/2021	n/a		
WS/2018/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>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</p>	20/05/2021	n/a		

WS/1994	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	11/03/2021	n/a		
WS/1988	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p>	11/03/2021	n/a		
WS/1912	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p>	26/11/2020	n/a		
WS/1878	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.b.2.e - Change in test procedure for AS or</p>	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	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits</p> <p>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</p> <p>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</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p>	22/10/2020	n/a		
WS/1826	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	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	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation</p> <p>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</p>	14/05/2020	n/a		
II/0141	Update of sections 4.2 and 5.1 of the Twinrix Paediatric 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 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). 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	10/03/2021	SmPC and Annex II	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 Twinrix Paediatric, showed anti-HAV seropositivity rates of 100% and anti-HBs seroprotection rates of 81.8%. These data show the long-term persistence of immune memory for both hepatitis A and B vaccination with Twinrix Paediatric, 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	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>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</p>	27/02/2020	n/a		
WS/1670	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.z - Quality change - Finished product - Other variation</p>	25/07/2019	n/a		
IG/1121	A.7 - Administrative change - Deletion of manufacturing sites	16/07/2019	n/a		

WS/1593	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation</p>	21/03/2019	n/a		
WS/1432	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	14/03/2019	n/a		
IG/1063/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p>	31/01/2019	n/a		

	<p>corresponding test method</p> <p>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</p>				
WS/1420	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	17/01/2019	n/a		
IG/0960	<p>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</p>	24/09/2018	13/09/2019	SmPC, Annex II, Labelling and PL	
WS/1365/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.a.2.a - Changes in the manufacturing process of</p>	05/07/2018	n/a		

	<p>the AS - Minor change in the manufacturing process of the AS</p> <p>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</p>				
IG/0921	<p>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</p>	08/05/2018	n/a		
WS/1237/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p>	22/02/2018	n/a		
WS/1240/G	<p>This was an application for a group of variations following a worksharing procedure according to</p>	09/11/2017	n/a		

	<p>Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p>				
WS/1223	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p>	09/11/2017	n/a		
N/0123	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	05/10/2017	n/a		



	<p>worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p>				
WS/1115/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>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)</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p>	18/05/2017	n/a		
WS/1046	<p>This was an application for a variation following a worksharing procedure according to Article 20 of</p>	16/02/2017	n/a		

	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				
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/0111	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	13/10/2017	SmPC, Annex II, Labelling and PL	
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.	21/09/2016	n/a		

	<p>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</p> <p>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</p> <p>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</p> <p>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</p>				
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/0109	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/11/2015	02/12/2015	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	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p>	22/01/2015	n/a		
WS/0610/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>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</p>	22/01/2015	n/a		
IB/0104	C.I.z - Changes (Safety/Efficacy) of Human and	14/01/2015	02/12/2015	SmPC, Annex	

	Veterinary Medicinal Products - Other variation			II, Labelling and PL	
IG/0499	A.7 - Administrative change - Deletion of manufacturing sites	05/12/2014	n/a		
WS/0603	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation</p>	20/11/2014	n/a		
WS/0591	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	20/11/2014	n/a		
WS/0593	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a</p>	23/10/2014	n/a		

	new specification parameter to the specification with its corresponding test method				
WS/0592	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>This was an application following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p>	26/06/2014	n/a		
WS/0515	This was an application for a variation following a	26/06/2014	n/a		

	<p>worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p>				
WS/0553	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p>	26/06/2014	n/a		
IG/0446	<p>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</p>	24/06/2014	n/a		
WS/0505/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	22/05/2014	n/a		



	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/0088	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	20/03/2014	n/a		

	<p>the product.</p> <ul style="list-style-type: none"> <li>-Scale up of active substance of vaccine.</li> <li>-Introduction of alternative containers for the active substance.</li> </ul> <p>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</p> <p>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</p> <p>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)</p> <p>B.I.c.1.b - Change in immediate packaging of the AS</p> <ul style="list-style-type: none"> <li>- Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs</li> </ul>				
WS/0415	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Change in specifications of active substance.</p>	23/01/2014	n/a		

	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	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Change in the specification parameters of a raw material .</p> <p>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</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>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)</p>	18/12/2013	n/a		
N/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2013	02/12/2015	PL	
WS/0443	This was an application for a variation following a	24/10/2013	n/a		

	<p>worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation</p>				
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/0077	<p>Replacement of the current screwcaps used for the purified bulk transfer and storage.</p> <p>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</p>	21/02/2013	n/a		
WS/0336	This was an application for a variation following a	17/01/2013	n/a		

	<p>worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>To introduce a new method for monitoring homogeneity during filling.</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p>				
WS/0239	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>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</p>	19/04/2012	n/a		
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	19/01/2012	n/a		

	<p>1234/2008.</p> <p>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.</p> <p>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</p>				
WS/0153	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	17/11/2011	13/01/2012	SmPC and PL	<p>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.</p> <p>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</p>

	<p>representatives in the PL of Pumarix, Ambirix, Pandemrix, Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals, Prepandrix and Fendrix.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>				<p>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.</p>
II/0065	<p>Update of section 4.8 of the SmPC to include immediate injection site pain, stinging and burning sensation. The PL is updated in accordance. 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.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	17/11/2011	13/01/2012	SmPC, Labelling and PL	<p>Following clusters of spontaneous reports of immediate onset injection site pain reported in certain batches of the preservative-free formulation of 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. 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 Paediatric remains positive.</p>
IB/0066	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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Registration of an additional facility for filling of finished product. The change relates to pre-filled</p>	20/10/2011	20/10/2011		

	<p>syringes only.</p> <p>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.</p>				
IG/0064/G	<p>This was an application for a group of variations.</p> <p>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.</p> <p>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</p>	04/05/2011	n/a		<p>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.</p>



	<p>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</p> <p>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</p> <p>B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier</p>				
IG/0052/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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)</p>	18/03/2011	n/a		
II/0062	<p>Registration of a new Hepatitis A working seed.</p> <p>B.I.a.2.c - Changes in the manufacturing process of</p>	16/12/2010	03/01/2011		

	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/0064	<p>To update section 4.5 of the SmPC based on a clinical trial (HPV-029) to evaluate the feasibility of co-administration of the HPV-16/18 L1 AS04 (Cervarix) and HAB vaccine (Twinrix Paediatric) with respect to immunogenicity, reactogenicity and safety, as compared to their separate administration, in healthy female subjects aged between 9 and 15 years of age.</p> <p>The MAH also took the opportunity of this variation to comply with the latest version of the QRD template and to update the details of the local representatives in EU countries in the PL.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	23/09/2010	05/11/2010	SmPC, Labelling and PL	To evaluate the feasibility of co-administration of Twinrix paediatric and Cervarix (a human papilloma virus (HPV) vaccine) a trial was ran to assess the impact immunogenicity, reactogenicity and safety, as compared to their separate administration, in healthy female subjects aged between 9 and 15 years of age. Results show that Twinrix paediatric may be administered concomitantly with Cervarix. Administration of Twinrix paediatric at the same time as Cervarix has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody titers were lower on co-administration, but the clinical significance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs $\geq 10\text{mIU/ml}$ was 98.3% for concomitant vaccination and 100% for Twinrix Paediatric alone.
II/0063	To update section 4.2 and 5.1 of the SmPC with data coming from two long-term immune persistence studies: HAB-137 and HAB-157 which were conducted in children 1 to 11 years old and in adolescents 12 to 15 years old respectively. The MAH took further the opportunity of this variation to fulfill its commitment to remove any reference to thiomersal containing formulations under sections 4.8 and 5.1 of the SmPC and to introduce minor typographical changes in the SmPC.	23/09/2010	05/11/2010	SmPC	<p>The MAH submitted two (HAB-137 and HAB-157) long-term immune persistence studies for Twinrix paediatric to update the product information with long-term persistence data up to 10 years post primary immunisation.</p> <p>The data from these studies suggest that administration of three doses of Twinrix Paediatric to healthy children aged 1-15 years at the time of the first vaccination results in high rates of persistence of detectable antibody to HAV and HBs. All subjects retained <math>\geq 15\text{ mIU/ml}</math> anti-HAV when followed for up to 5-10 years. The majority retained <math>\geq 10</math></p>

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				mIU/ml anti-HBs at these same time points. Those who had ant-HBs below this cut-off at some stage and received Engerix B (of content appropriate to their age) responded to the challenge dose. The Product Information was updated to reflect these findings.
II/0061	To update the internal monograph for a raw material used in the manufacture 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	Change in cell identity method.  Change to the test procedure and/or specification of a raw material	17/12/2009	07/01/2010		

II/0059	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/0058	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	18/09/2009	n/a		
IB/0057	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	20/07/2009	n/a		
II/0055	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/0056	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	19/06/2009	n/a		
IA/0054	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/02/2009	n/a		
IA/0053	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/07/2008	n/a		
II/0050	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

	<p>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.</p> <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p>				<p>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.</p>
IA/0052	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	07/05/2008	n/a		
II/0049	<p>Update of Summary of Product Characteristics and Package Leaflet.</p> <p>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 Paediatric 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 correct a mistake in section 4.2 of the SPC for the pre-filled syringes, to update the contact details for the local representatives of Romania and Slovakia in the PL and to make minor changes in the</p>	13/12/2007	22/01/2008	SmPC and PL	<p>Based on an analysis of pooled safety data from 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, 'hypoesthesia' (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. 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</p>

	SPC in line with the EMEA/QRD template version 7.2.  Update of Summary of Product Characteristics and Package Leaflet				the adverse events reported following overdosage were similar to those reported with normal vaccine administration.
IA/0051	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	07/12/2007	n/a		
II/0048	Change(s) to the manufacturing process for the finished product	16/11/2006	22/11/2007		
II/0047	Change(s) to the manufacturing process for the active substance	16/11/2006	04/01/2007	SmPC, Labelling and PL	
R/0046	Renewal of the marketing authorisation.	28/06/2006	28/08/2006	SmPC, Annex II, Labelling and PL	
II/0042	Change(s) to the manufacturing process for the active substance	27/04/2006	03/05/2006		
II/0043	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/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2005	n/a	Labelling and PL	
IA/0044	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	01/08/2005	n/a		

N/0041	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: Czech, Danish, German, Greek, Spanish, Hungarian, Icelandic, Italian, 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/0040	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/03/2004	n/a		
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/10/2003	15/12/2003	Labelling and PL	
II/0036	Quality changes	22/10/2003	27/10/2003		
II/0035	Quality changes	22/10/2003	27/10/2003		
II/0034	Change(s) to the test method(s) and/or specifications for the finished product	25/09/2003	02/10/2003		
I/0038	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	18/07/2003	23/07/2003		
II/0033	Change(s) to the test method(s) and/or	20/02/2003	10/03/2003		

	specifications for the active substance				
II/0029	Update of Summary of Product Characteristics and Package Leaflet	27/06/2002	24/10/2002	PL	
I/0032	31_Change in container shape	20/09/2002	27/09/2002		
II/0031	Change(s) to shelf-life or storage conditions	25/07/2002	02/09/2002		
II/0030	Quality changes	25/07/2002	02/09/2002		
II/0027	Update of Summary of Product Characteristics	17/01/2002	11/04/2002	SmPC	
II/0028	Change(s) to the test method(s) and/or specifications for the finished product	21/03/2002	03/04/2002		
I/0025	30_Change in pack size for a medicinal product	07/11/2001	06/02/2002	SmPC and Labelling	
I/0024	30_Change in pack size for a medicinal product	07/11/2001	06/02/2002	SmPC and Labelling	
I/0023	03_Change in the name and/or address of the marketing authorisation holder 01_Change following modification(s) of the manufacturing authorisation(s)	05/11/2001	18/12/2001	SmPC, Annex II, Labelling and PL	
I/0026	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	28/11/2001		
I/0022	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	28/11/2001		



R/0021	Renewal of the marketing authorisation.	26/07/2001	09/11/2001	SmPC, Annex II, Labelling and PL	
II/0019	Update of or change(s) to the pharmaceutical documentation	20/09/2001	20/10/2001		
II/0020	Update of Summary of Product Characteristics	26/04/2001	30/08/2001	SmPC	
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/03/2001	03/05/2001	Labelling	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	19/10/2000	20/03/2001	SmPC and PL	
I/0018	30_Change in pack size for a medicinal product	11/12/2000	05/03/2001	SmPC, Labelling 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 manufacturing process for the active substance	29/06/2000	27/07/2000		
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	29/07/1999	13/09/1999		

	active substance				
I/0010	13_Batch size of active substance	29/07/1999	10/09/1999		
I/0009	31_Change in container shape	26/05/1999	09/07/1999		
I/0008	25_Change in test procedures of the medicinal product	25/03/1999	18/05/1999		
I/0005	20_Extension of shelf-life as foreseen at time of authorisation	06/11/1998	26/01/1999	SmPC	
I/0007	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	31/12/1998	14/01/1999		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/10/1998	22/12/1998	PL	
II/0002	Change(s) to container	23/07/1997	19/11/1997	Labelling	
I/0004	01_Change following modification(s) of the manufacturing authorisation(s)	31/10/1997	n/a		
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		