Infanrix hexa

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/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	31/08/2023	n/a		

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

	- 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)				
IA/0336	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	21/08/2023	n/a		
IA/0333/G	This was an application for a group of variations. 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	07/07/2023	n/a		
WS/2476	This was an application for a variation following a worksharing procedure according to Article 20 of	06/07/2023	n/a		

	Commission Regulation (EC) No 1234/2008. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				
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/2456/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.z - Change in test procedure for the finished product - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	01/06/2023	n/a		
IB/0330	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	28/04/2023		SmPC	
WS/2365	This was an application for a variation following a worksharing procedure according to Article 20 of	26/04/2023		SmPC, Annex II, Labelling	The SmPC Section 4.4 (Bexsero), 6.5 and 6.6 has been updated as follows:

	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			and PL	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/2425/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.z - Change in test procedure for the finished product - Other variation B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/03/2023	n/a		
WS/2424/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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.4.z - Change to in-process tests or limits	16/03/2023	n/a		

	applied during the manufacture of the AS - Other variation B.II.c.2.z - Change in test procedure for an excipient - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				
WS/2423	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	09/03/2023	n/a		
IG/1584	A.7 - Administrative change - Deletion of manufacturing sites	02/03/2023	n/a		
WS/2384	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	09/02/2023	n/a		
WS/2393	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	09/02/2023	n/a		

	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				
WS/2371	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	09/02/2023	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/2347/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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition	20/10/2022	n/a		

	of a new in-process test and limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
WS/2300/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.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.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.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile) B.I.d.1.b.2 - Stability of AS - Change in the storage conditions - Change in storage conditions of biological/immunological ASs, when the stability	08/09/2022	n/a		

	studies have not been performed in accordance with a currently approved stability protocol B.I.d.1.a.3 - Stability of AS - Change in the re-test period/storage period - Extension of storage period of a biological/immunological AS not in accordance with an approved stability protocol				
WS/2296/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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	08/09/2022	n/a		
WS/2258/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	23/06/2022	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
WS/2232/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.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	19/05/2022	n/a		
II/0309/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.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	07/04/2022	n/a		

	biol. reference preparation not covered by an approved protocol				
WS/2183	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. In addition, the MAH took the opportunity to align the PI to the Annex to the European Commission guideline on "Excipients in the labelling and package leaflet of medicinal product for human use" (sections 2, 4.4 and 6.1 of the SmPC). The Package Leaflet is updated accordingly. The MAH also took the opportunity to introduce some additional minor changes to the PI and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/03/2022	03/02/2023	SmPC, Labelling and PL	Update of section 2 of the SmPC of Infanrix Hexa. The PI was aligned to the Annex of the European Commission guideline on "Excipients in the labelling and package leaflet of medicinal product for human use" (sections 2, 4.4 and 6.1 of the SmPC). The Package Leaflet was updated accordingly. For more information, please refer to the Summary of Product Characteristics.
IB/0313	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	18/02/2022	n/a		
WS/2199	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.c - Change in test procedure for the finished product - Substantial change to or replacement of a	17/02/2022	n/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				
IG/1474/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	07/02/2022	n/a		
WS/2140	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	13/01/2022	n/a		
WS/2132	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.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	02/12/2021	n/a		
WS/2147	This was an application for a variation following a	25/11/2021	n/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				
IG/1449	A.7 - Administrative change - Deletion of manufacturing sites	09/11/2021	n/a		
WS/2094	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	09/09/2021	n/a		
IA/0304/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	02/09/2021	n/a		

	manufacturing sites				
IA/0303	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	03/08/2021	n/a		
WS/2087	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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	22/07/2021	n/a		
WS/2053	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	24/06/2021	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		
PSUSA/1122/	Periodic Safety Update EU Single assessment -	10/06/2021	n/a		PRAC Recommendation - maintenance

202010	diphtheria / tetanus / pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) (acellular, component) / hepatitis b (rdna) / poliomyelitis (inactivated) / haemophilus type b conjugate vaccines (adsorbed)				
WS/2012/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.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/05/2021	n/a		
WS/2024	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.z - Change in the specification parameters and/or limits of the finished product - Other variation	29/04/2021	n/a		

IG/1379	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	30/03/2021	n/a		
WS/2014	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	25/03/2021	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/1987	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.z - Change in container closure system of the Finished Product - Other variation	11/02/2021	n/a		

WS/1973	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.z - Quality change - Finished product - Other variation	04/02/2021	n/a		
WS/1960	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.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	04/02/2021	n/a		
N/0288	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/01/2021	16/09/2021	Labelling	
WS/1954	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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	14/01/2021	n/a		
WS/1890	This was an application for a variation following a worksharing procedure according to Article 20 of	10/12/2020	n/a		

	Commission Regulation (EC) No 1234/2008. B.I.b.z - Change in control of the AS - Other variation				
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 starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	26/11/2020	n/a		
WS/1905	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)	26/11/2020	n/a		

WS/1913/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.z - Changes in the manufacturing process of the AS - Other variation B.I.b.z - Change in control of the AS - Other variation	06/11/2020	n/a		
IA/0287/G	This was an application for a group of variations. 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	29/10/2020	n/a		
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	22/10/2020	n/a		

	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				
WS/1838	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	03/09/2020	n/a		
II/0275	Update of sections 4.8 and 5.1 of the SmPC in relation to the frequency of adverse reactions somnolence (from uncommon to very common) and fatigue (from very common to uncommon) and to update the safety and immunogenicity information in infants and toddlers born to mothers vaccinated with dTpa during pregnancy; based on data generated from DTPA-048 and DTPA-049; these are phase IV, open-label, non-randomised, multicentre studies aimed to provide immunological responses to Infanrix hexa in terms of seroprotection status for diphtheria (D), tetanus (T), HBs antigen, inactivated poliovirus (IPV) and Haemophilus influenzae type b (Hib) antigens (PRP) and in terms of vaccine or booster responses to the pertussis antigens, 1 month	03/09/2020	16/09/2021	SmPC and PL	Maternal immunisation has proved its benefit in protecting neonates against (severe) pertussis disease during the first months of life. Based on data generated from DTPA-048 and DTPA-049, post-primary and post-booster vaccination, immunological data did not show clinically relevant interference of maternal vaccination with diphtheria, tetanus, acellular pertussis (dTpa) on the infant's and toddler's responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, Haemophilus influenzae type b or pneumococcal antigens. Lower antibody concentrations against pertussis antigens post-primary (PT, FHA and PRN) and post-booster (PT, FHA) vaccination were observed in infants and toddlers

	after the last dose of the primary vaccination or the booster dose. The MAH took the opportunity to update the posology information in the package leaflet to align it with the SmPC. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and 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				born to mothers vaccinated with dTpa during pregnancy. The fold-increases of anti-pertussis antibody concentrations from the pre-booster to the 1-month post-booster time point were in the same range for infants and toddlers born to mothers vaccinated with dTpa or with placebo, demonstrating effective priming of the immune system. In the absence of correlates of protection for pertussis, the clinical relevance of these observations remains to be fully understood. However, current epidemiological data on pertussis disease following the implementation of dTpa maternal immunisation do not suggest any clinical relevance of this immune interference. The MAH also took the opportunity to update the frequency for "Fatigue" (from very common to uncommon) and "Somnolence" (from uncommon to very common) as a result of the reencoding "Drowsiness" under the MedDRA Preferred Term from "Fatigue" to "Somnolence". For more information, please refer to the Summary of Product Characteristics.
IA/0280	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	18/08/2020	n/a		
WS/1812	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	23/07/2020	n/a		

	(including replacement or addition)				
WS/1817/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.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/07/2020	n/a		
IA/0278	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	29/05/2020	n/a		
WS/1785/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.a - Change to in-process tests or limits	28/05/2020	n/a		

	applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test				
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		
WS/1781/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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	07/05/2020	n/a		

WS/1770/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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	23/04/2020	n/a		
WS/1758	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.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	12/03/2020	n/a		
WS/1725	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	23/01/2020	n/a		

	material/intermediate				
WS/1691/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.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.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	16/01/2020	n/a		
IA/0269	A.7 - Administrative change - Deletion of manufacturing sites	17/12/2019	n/a		
WS/1694	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	12/12/2019	n/a		

	(including replacement or addition)				
WS/1684/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/12/2019	n/a		
IA/0268	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	04/12/2019	13/01/2020	SmPC, Labelling and PL	
WS/1673	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	14/11/2019	n/a		
IA/0262	A.7 - Administrative change - Deletion of manufacturing sites	26/07/2019	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.	25/07/2019	n/a		

	B.II.z - Quality change - Finished product - Other variation				
WS/1585	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	11/07/2019	n/a		
WS/1594	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)	20/06/2019	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		
WS/1498/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	04/04/2019	n/a		

	1234/2008. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation 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.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation				
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/1534	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.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	14/03/2019	n/a		
WS/1515	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	14/02/2019	n/a		
WS/1497/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.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	14/02/2019	n/a		

II/0250	Update of section 5.1 of the SmPC in order to add information on the persistence of immunity against hepatitis B up to 14-15 years of age, based on results from study DTPa-HBV-IPV-115. This was a phase IV, open-label, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a challenge dose of hepatitis B vaccine (Engerix-B Kinder SKF103860) in children aged 14-15 years, previously primed and boosted in the first two years of life with four doses of GSK Biologicals' DTPa-HBV-IPV/Hib (Infanrix hexa SB217744) vaccine. In addition, in line with the SmPC Guideline, the MAH took the opportunity to introduce in section 4.1 of the SmPC a statement regarding the use of Infanrix hexa in accordance with official recommendations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	07/02/2019	13/01/2020	SmPC	Long-term persistence of seroprotective antibody concentrations against HBV was observed in approximately half of the adolescents aged 14-15 years who received 4 doses of Infanrix hexa during infancy. Despite half of the subjects having antibody levels below the seroprotection threshold of ≥10 mIU/ml, an anamnestic response to a challenge dose of monovalent HBV vaccine was shown in more than 90% of subjects. The results suggested that protective immune memory persists in the majority of subjects up to 14-15 years of age. In addition, the results indicated that the long-term immune response to hepatitis B component of the Infanrix hexa vaccine is comparable to the immune response to monovalent HBV vaccine.
IG/1063/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method	31/01/2019	n/a		

	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/1475	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.2 - Introduction of a post approval change management protocol related to the AS	17/01/2019	n/a		
WS/1471/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)	13/12/2018	n/a		
WS/1456	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	08/11/2018	n/a		

	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				
WS/1442	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.z - Changes in the manufacturing process of the AS - Other variation	18/10/2018	n/a		
WS/1435/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.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	18/10/2018	n/a		

WS/1387	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	18/10/2018	n/a		
WS/1421	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.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	04/10/2018	n/a		
WS/1410	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	13/09/2018	n/a		
WS/1377/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	19/07/2018	n/a		

	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation				
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	05/07/2018	n/a		

	1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
PSUSA/1122/ 201710	Periodic Safety Update EU Single assessment - diphtheria / tetanus / pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) (acellular, component) / hepatitis b (rdna) / poliomyelitis (inactivated) / haemophilus type b conjugate vaccines (adsorbed)	14/06/2018	n/a		PRAC Recommendation - maintenance
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		
II/0235	Update of section 4.5 of the SmPC in order to update the interactions section with additional data on the co-administration with Meningococcal serogroup B vaccine (MenB) in order to facilitate the	12/04/2018	23/01/2019	SmPC	Infanrix hexa can be given concomitantly with meningococcal serogroup B vaccine (MenB). When Infanrix hexa was co-administered with MenB and pneumococcal conjugate vaccines, inconsistent results were seen across

	administration of Infanrix hexa and Bexsero to infants and toddlers based on final results from clinical studies V72P12, V72P13 and V72P16. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				studies for responses to inactivated poliovirus type 2, pneumococcal conjugate serotype 6B antigen and to the pertussis pertactin antigen but these data do not suggest clinically significant interference. Due to an increased risk of fever, pain at the injection site, appetite lost and irritability when Infanrix hexa was co-administered with MenB vaccine and 7-valent pneumococcal conjugate vaccine, separate vaccinations can be considered when possible.
II/0237/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile)	15/03/2018	23/01/2019	Annex II	

WS/1237/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	22/02/2018	n/a		
WS/1232	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	15/02/2018	n/a		
WS/1297	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	08/02/2018	n/a		

	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0234	Update of section 5.1 of the SmPC in order to update the safety information regarding the long term immunity persistence to Hepatitis B at 12/13 years based on the final study CSR DTPa-HBV-IPV-114 in the framework of art. 46 submission (procedure number EMEA/H/C/000296/P46/117). In addition, minor editorial updates are included in section 4.4 of the SmPC to improve clarity. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/02/2018	23/01/2019	SmPC	With regards to hepatitis B, protective immunity (≥10 mIU/ml) following a 3-dose primary and booster schedule with Infanrix hexa has been shown to persist in ≥ 85% of subjects 4-5 years of age, in ≥72% of subjects 7-8 years of age and in ≥60% of subjects 12-13 years of age. Additionally, following a 2-dose primary and booster schedule, protective immunity against hepatitis B persisted in ≥ 48% of subjects 11-12 years of age.
WS/1255	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.z - Quality change - Active substance - Other variation	14/12/2017	n/a		
WS/1250/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.z - Changes in the manufacturing process of the AS - Other variation	14/12/2017	n/a		

	B.I.c.1.z - Change in immediate packaging of the AS - Other variation				
WS/1257	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.z - Quality change - Active substance - Other variation	14/12/2017	n/a		
WS/1245	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	30/11/2017	n/a		
WS/1239/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	09/11/2017	n/a		

	B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.z - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Ph. Eur. TSE Certificate of suitability - Other variation				
WS/1223	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/11/2017	n/a		
WS/1227	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	02/11/2017	n/a		
WS/1215	This was an application for a variation following a	19/10/2017	n/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				
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/1194	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	14/09/2017	n/a		
WS/1172	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	14/09/2017	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				
IB/0220	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/07/2017	11/09/2017	SmPC, Labelling and PL	
WS/1166	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	22/06/2017	n/a		
WS/1150/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.e.2 - Introduction of a post approval change	22/06/2017	n/a		

	management protocol related to the AS				
WS/1116	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.c.1.z - Change in immediate packaging of the AS - Other variation	05/05/2017	n/a		
WS/1048/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.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	23/03/2017	n/a		
WS/0972/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.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	09/03/2017	n/a		

	material/intermediate/reagent - Other variation B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
WS/1068/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.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP 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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	23/02/2017	n/a		
WS/1069/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.	23/02/2017	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 B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation				
WS/1067/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.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation	16/02/2017	n/a		
WS/1049	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	26/01/2017	11/09/2017	SmPC and PL	
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-	16/12/2016	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter)				
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		
WS/0976/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.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.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	15/12/2016	n/a		
WS/0969	This was an application for a variation following a worksharing procedure according to Article 20 of	24/11/2016	n/a		

	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				
IG/0721	A.7 - Administrative change - Deletion of manufacturing sites	10/10/2016	n/a		
WS/0970	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	22/09/2016	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	21/09/2016	n/a		

	B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
IA/0207	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	20/09/2016	11/09/2017	Annex II	
II/0202/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a	15/09/2016	11/09/2017	SmPC, Annex II, Labelling and PL	

	biological/immunological AS 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 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 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 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 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 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				
IA/0201	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	09/06/2016	n/a		
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		
IA/0199	B.I.b.1.d - Change in the specification parameters	19/05/2016	n/a		

	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/0916	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.h.1.b.2 - Update to the Adventitious Agents Safety Evaluation information - Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier - without modifications of risk assessment	12/05/2016	n/a		
IA/0198	A.7 - Administrative change - Deletion of manufacturing sites	04/05/2016	n/a		
WS/0876	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.z - Change in the specification parameters and/or limits of the finished product - Other variation	01/04/2016	n/a		
WS/0854/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.d - Change in the specification parameters	04/02/2016	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
WS/0828	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	17/12/2015	n/a		
IA/0195/G	This was an application for a group of variations. 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.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	09/12/2015	n/a		
IA/0194	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	09/12/2015	n/a		

	corresponding test method				
II/0190	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	26/11/2015	n/a		
WS/0819	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	19/11/2015	n/a		
IB/0192	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	28/10/2015	n/a		
II/0178	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include more information on the use of Infanrix hexa in premature infants. In addition, some lay-out changes are proposed in Annex II. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/10/2015	SmPC and Annex II	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include information on the use of Infanrix hexa in premature infants. In addition, some lay-out changes (addition of bullets) are proposed in Annex II.

WS/0794/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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	15/10/2015	n/a		
WS/0788	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	01/10/2015	n/a		
II/0180	Update of section 5.1 of the SmPC in order to describe the results of the Hepatitis B immunity persistence data gathered. C.I.4 - Change(s) in the SPC, Labelling or PL due to	24/09/2015	28/10/2015	SmPC	This submission intends to describe the results of the Hepatitis B immunity persistence data gathered so far in the Summary of Product Characteristics of Infanrix hexa, section 5.1 'Pharmacodynamic properties'. Moreover, studies DTPa-HBV-IPV-110 and -111 also

	new quality, preclinical, clinical or pharmacovigilance data				evaluated the persistence of the immune response induced by Infanrix hexa against diphtheria, tetanus, pertussis, poliovirus and Haemophilus influenzae type b. Update of section 5.1 of the SmPC in order to describe the results of the Hepatitis B immunity persistence data gathered.
II/0179	Update of sections 2 and 5.1 of the SmPC to add data generated in study DTPa-HBV-IPV/Hib-MenC-TT-003 for the new 2+1 schedule (2, 4 and 12 months of age). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/10/2015	SmPC	In the clinical study DTPa-HBV-IPV/Hib-MenC-TT-003, Infanrix hexa co-administered with Prevenar 13, Menjugate and Rotarix was administered to infants randomized to the control group and the vaccines were administered according to a 2+1 schedule, with two primary vaccination doses at 2 and 4 months of age and a booster dose at 12 months of age. This submission intends to include the immunogenicity data generated in this study for the new 2+1 schedule (2, 4 and 12 months of age) in the SmPC, section '5.1 Pharmacodynamic properties'. Update of sections 2 and 5.1 to add data generated in study DTPa-HBV-IPV/Hib-MenC-TT-003 for the new 2+1 schedule (2, 4 and 12 months of age).
II/0177	Update of sections 4.4, 4.5 and 4.8 of the SmPC in order to update the safety information of Infanrix hexa on the co-adminstration with several other paediatric vaccines. In addition, the MAH is updating the details for some of the local representatives. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/10/2015	SmPC and PL	Update of sections 4.4, 4.5 and 4.8 of the SmPC in order to update the safety information of Infanrix hexa on the co-administration with several other paediatric vaccines. The package leaflet has been amended accordingly.
WS/0775	This was an application for a variation following a worksharing procedure according to Article 20 of	17/09/2015	n/a		

	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				
PSUSA/1122/201410	Periodic Safety Update EU Single assessment - diphtheria / tetanus / pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) (acellular, component) / hepatitis b (rdna) / poliomyelitis (inactivated) / haemophilus type b conjugate vaccines (adsorbed)	25/06/2015	20/08/2015	SmPC, Annex II, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1122/201410.
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		
WS/0730	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	25/06/2015	n/a		

	starting material/reagent/intermediate - Other variation				
WS/0732	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		
IB/0181	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	23/04/2015	n/a		
WS/0430/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.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method 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	23/04/2015	n/a		

WS/0681	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.3 - Stability of AS - Change in the re-test period/storage period - Extension of storage period of a biological/immunological AS not in accordance with an approved stability protocol	26/03/2015	n/a		
WS/0680	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.3 - Stability of AS - Change in the re-test period/storage period - Extension of storage period of a biological/immunological AS not in accordance with an approved stability protocol	26/03/2015	n/a		
IA/0175	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)	10/02/2015	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	22/01/2015	n/a		

	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				
IG/0499	A.7 - Administrative change - Deletion of manufacturing sites	05/12/2014	n/a		
IG/0498	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	21/11/2014	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. 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.	20/11/2014	n/a		

	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		
II/0154	Update of sections 4.4, 4.5 and 4.8 of the SmPC with information that increased rates of convulsions and hypotonic hyporesponsive episodes are observed with concomitant administration with Prevenar 13 vaccine in follow up to the outcome of a PSUR assessment for Prevenar 13. Section 2 of the package leaflet on warnings and precautions is updated to reflect the changes of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	20/08/2015	SmPC and PL	The MAH has provided analyses of post-marketing reports when Infanrix hexa is co-administered with Prevenar (pneumococcal saccharide conjugated vaccine, adsorbed). Results show an increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) with concomitant administration of Infanrix hexa and Prevenar 13.
WS/0595	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/09/2014	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				
IB/0167	B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	01/09/2014	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		
IG/0468	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/0566	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	24/07/2014	n/a		
WS/0565	This was an application for a variation following a	24/07/2014	n/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				
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		

WS/0498/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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	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		
IAIN/0160	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	17/06/2014	30/09/2014	SmPC, Labelling and PL	
WS/0512/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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or	22/05/2014	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/0521	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	22/05/2014	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		

II/0139	Update of section 5.1 of the SmPC with data from routine surveillance of Haemophilus influenzae type b (Hib) disease in Italy. In addition, reference to official recommendations is included in section 4.2 of the SmPC and the presentation of data is simplified in section 5.1 of the SmPC. Section 4.8 of the SmPC was revised according to the SmPC guideline. Furthermore, the PI is being brought in line with the latest QRD template version 9. Following CHMP request section 2 of the SmPC was updated to include traces of formaldehyde, neomycin and polymyxin which are used during the manufacturing process and section 4.3 was revised accordingly to add formaldehyde. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	30/09/2014	SmPC, Annex II, Labelling and PL	Results of ongoing routine national surveillance in Italy demonstrate that Infanrix hexa is effective in controlling Hib disease in infants when the vaccine is administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 11 months. Over a six year period starting in 2006, where Infanrix hexa was the principal Hib-containing vaccine in use with vaccination coverage exceeding 95%, Hib invasive disease continued to be well controlled, with four confirmed Hib cases reported in Italian children aged less than 5 years through passive surveillance.
WS/0499	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	25/04/2014	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/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/0494	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	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		
WS/0445/G	This was an application for a group of variations	20/03/2014	n/a		

	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 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				

II/0138	Addition to the Product Information of clear guidance for Health professionals regarding the use of the vaccine in case of accidental temperature excursion and other minor changes to improve handling instructions. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	30/09/2014	SmPC and PL	
WS/0478/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.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	20/02/2014	n/a		
WS/0441	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes in the manufacturing process of the active substance. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	20/02/2014	n/a		

	of the AS				
WS/0419/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 a test procedure for quality control testing of active substances. - Change in the specification parameters for active substances. 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.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.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.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	23/01/2014	n/a		

	material/intermediate 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.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				
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		
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/0420	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in the immediate packaging of the active substance. 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	21/11/2013	n/a		
WS/0443	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other	24/10/2013	n/a		

	variation				
WS/0381	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.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	24/10/2013	n/a		
IAIN/0137	C.I.10 - Change in the frequency and/or date of submission of PSURs for human medicinal products	15/10/2013	30/09/2014	Annex II	
II/0131	Introduction of a post approval change management protocol related to the AS. B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	25/07/2013	n/a		
WS/0401	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	25/07/2013	n/a		

WS/0392	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To replace the current FHA reference standard with a new lot. 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	27/06/2013	n/a		
IG/0306	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2013	n/a		
WS/0384	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 working seed lot used for the manufacturing process of the acellular pertussis (Pa) antigens. 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	30/05/2013	n/a		
IG/0297	C.I.z - Changes (Safety/Efficacy) of Human and	19/04/2013	n/a		

	Veterinary Medicinal Products - Other variation				
II/0125	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		
IG/0265/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	28/01/2013	n/a		
WS/0340	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change of specifications of reagent. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	17/01/2013	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		
II/0120/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. 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	21/06/2012	n/a		
WS/0239	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Registration of an additional site for QC sterility testing activities for pre-filled syringes, following a worksharing procedure according to Article 20 of	19/04/2012	n/a		

	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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	19/01/2012	n/a		

	procedure				
IG/0133	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	22/11/2011	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/0106	To update section 5.1 of the SmPC based on the final report of the ESPED study (Hib effectiveness study) covering seven years of post-licensure surveillance. The MAH has also taken the opportunity to make some changes in relation to the QRD template, formatting changes and typos correction. The details of the Czech and Maltese local representatives are also revised in the package leaflet. Annex A is also revised to provide a more precise value for the quantity of tetanus toxoid carrier contained in the	23/06/2011	26/07/2011	SmPC, Labelling and PL	The Marketing Authorisation Holder has provided the final report of a case-cohort study performed by the ESPED study group and conducted in Germany to estimate vaccine effectiveness of the Hib component against Hib disease. The study covered the years 2001-2007 (seven years of surveillance associated to the use of the hexavalent vaccines). The effectiveness of the Hib component of two hexavalent vaccines, of which one was Infanrix hexa, was 89.6% (95% CI: 74.4-95.8) for a full primary series and 100% (95% CI:

	vaccine. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				99.9-100.0) for a full primary series plus booster dose, irrespective of the Hib vaccine used for priming. Effectiveness was 78.9% (95% CI: 47.2-91.5) for an incomplete primary series, and 100% (95% CI: 99.7-100.0) for a 2nd year dose without full immunisation. Vaccine effectiveness for DTaP-IPV-HB/Hib combination vaccines against invasive Hib was 92.8% (95% CI: 82.3-97.1) for children vaccinated according to their age and to the German recommended vaccination schedule. Section 5.1 of the SmPC has been updated to reflect the results of this surveillance study.
IG/0081	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	07/07/2011	n/a		
WS/0113	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes to the manufacturing process of the FHA and PRN acellular pertussis antigens. 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	19/05/2011	19/05/2011		
IG/0064/G	This was an application for a group of variations. Update of section 4.8 of the SmPC to include immediate injection site pain, stinging and burning	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

	sensation. The PL is updated in accordance. The MAH has also taken the opportunity to align section 4.6 of the prefilled syringe presentation with the vial presentation. Furthermore, the Labelling is updated to specify the container 'prefilled syringe'. In addition, the MAH has taken the opportunity to update the list of local representatives in the PL. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test 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				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.

IG/0062/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	27/04/2011	n/a		
IG/0052/G	This was an application for a group of variations. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	18/03/2011	n/a		
IA/0105	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	04/03/2011	n/a	SmPC, Annex II, Labelling	

				and PL	
IB/0104/G	This was an application for a group of variations. Change to a test procedure for the active substance and the finished product. 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)	07/01/2011	n/a		
II/0103	A change in the manufacturing process for Pertussis toxoid. 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	21/12/2010		
II/0099	Changes to the manufacturing process of the diphteria drug substance. 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	21/10/2010	29/10/2010		

R/0097	Renewal of the marketing authorisation.	24/06/2010	31/08/2010	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Infanrix hexa continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of Infanrix hexa continues to be favourable. The CHMP therefore recommended that a renewal can be granted for unlimited validity. With this procedure the MAH also updated the product information (PI) to be in line with the current QRD requirements, to reflect the results of the user testing and to revise the contact details for Denmark.
IB/0102	Change in an in-process test for the active substance. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	11/08/2010	n/a		
IB/0100	Change in a test procedure for the master and working seeds of Clostridium tetani and Corynebacterium dipheriae. 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	11/08/2010	n/a		
IA/0101	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	04/08/2010	n/a		

IB/0098	To add a vial filling line located in Building WN16 at GSKBio's Wavre site. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	08/06/2010	n/a		
X/0095	To add a new pharmaceutical form Annex I_2.(d) Change or addition of a new pharmaceutical form	18/02/2010	10/05/2010	SmPC, Annex II, Labelling and PL	
II/0096	To introduce a change in the manufacturing process of the finished product. B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	22/04/2010	28/04/2010		
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	22/04/2010	22/04/2010		

	biological/immunological medicinal products.				
II/0094	To change the test for moisture content. Change(s) to the test method(s) and/or specifications for the finished product	18/02/2010	01/03/2010		
II/0093	Change in cell identity method. Change to the test procedure and/or specification of a raw material	17/12/2009	08/01/2010		
IB/0092	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	18/09/2009	n/a		
IB/0091	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	20/07/2009	n/a		
II/0090	Change to the primary pack stopper and tip cap for pre-filled syringes. Change(s) to the manufacturing process for the finished product	25/06/2009	06/07/2009		
II/0089	Introduction of new filter equipment during the manufacturing process of tetanus toxoid. Change(s) to the manufacturing process for the active substance	25/06/2009	06/07/2009		
II/0085	Modification of the purification process for tetanus	19/03/2009	24/03/2009		

	toxoid. Change(s) to the manufacturing process for the active substance				
II/0084	Change to the purification process of diphteria (D) and tetanus (T) toxoid. Change(s) to the manufacturing process for the active substance	19/03/2009	24/03/2009		
II/0086	Changes to raw materials used in the manufacturing process of the Inactivated Polio Virus antigens. Change to the test procedure and/or specification of a raw material	19/02/2009	04/03/2009		
IB/0087	IB_20_c_Change in test procedure for an excipient - other changes	11/02/2009	n/a		
IA/0088	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/02/2009	n/a		
IB/0083	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	23/12/2008	n/a		
IA/0082	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	18/11/2008	n/a		
II/0073	Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SPC based on a review of data available from clinical	26/06/2008	31/10/2008	SmPC, Annex II, Labelling	Based on data from clinical trials and post marketing setting the product information was updated in order to

	studies or post-marketing surveillance and in line with relevant guidelines. The PL was updated accordingly. In addition, the previously agreed class wording on apnoea was reflected in the PL as requested by the CHMP in July 2008. The MAH also took the opportunity to update all annexes (including labelling and annex II) in line with the latest version of the EMEA/QRD templates and to update the contact details of some local representatives in the PL (Romania, Slovakia). Update of Summary of Product Characteristics, Labelling and Package Leaflet			and PL	clarify the prescribing information and extend the advice provided to the health care provider. Premature infants might be vaccinated. However, a lower immune response may be observed. A warning was included to remind prescribers that the level of protection in these premature infants is currently not known. The undesirable effects section was fully reorganised in accordance with the frequency and seriousness of the events that have been reported. This means that some events were moved, reworded or deleted if not applicable. The following adverse events were added as reported in the post marketing setting: apnoea, in line with the warning which had been added following a variation that affected all infant vaccines; and injection site vesicles, lymphadenopathy and angioedema, as some cases were reported for which an alternative cause could not be established. Wording on persistence of protective antibodies against Hepatitis B was included in the product information. Further to the SPC update regarding the potential risk of apnoea in very premature infants, the PL was updated to inform that in babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination. All annexes (SPC, annex II, labelling and PL) were updated in line with the latest version of the EMEA/QRD templates. The contact details for Romania and Slovakia were updated.
II/0075	Update of section 5.1 of the SPC with information from a pertussis vaccine surveillance and effectiveness study in Sweden.	26/06/2008	08/08/2008	SmPC	The effectiveness of several acellular pertussis-based combined vaccines was assessed via a long-term surveillance study in Sweden. Results over eight years of

	Update of Summary of Product Characteristics				follow-up (1997-2005) showed that acellular pertussis vaccines are effective in infants vaccinated according to the 3-5-12 month vaccination schedule (i.e. primary vaccination at 3 and 5 months, booster dose at 12 months). However, protection against pertussis may be waning at 7-8 years of age with. Therefore, a second booster dose of pertussis vaccine may be needed in children aged 5-7 years who have previously been vaccinated according to this schedule.
II/0074	Update of section 5.1 of the SPC with information on the effectiveness of the Haemophilus influenzae type b (Hib) component of the vaccine based on the five-year results from a surveillance study in Germany. The MAH also took the opportunity to update the contact details of some local representatives in the PL and to make a correction in the PL regarding vaccination schedule to bring it in line with the SPC. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	08/08/2008	SmPC and PL	The effectiveness of the Hib component of Infanrix hexa and of another hexavalent vaccine was assessed via a surveillance study on Haemophilus influenzae disease in Germany. Over five years of follow-up (2001-2005), the effectiveness of hexavalent vaccines against invasive Hib infection was 68.4% for children receiving less than 3 doses in the first year of life without booster (i.e. incomplete primary series) and 90.4% for the full primary series. For the second year dose, vaccine effectiveness was 100.0% (regardless of priming). These results confirmed the high effectiveness of hexavalent vaccines against invasive Hib disease.
IA/0081	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/0076	Change(s) to the test method(s) and/or specifications for the active substance	30/05/2008	05/06/2008		
II/0071	Change(s) to the manufacturing process for the active substance	30/05/2008	05/06/2008		

II/0079	Change(s) to the manufacturing process for the finished product	24/04/2008	05/05/2008		
II/0078	Change(s) to the test method(s) and/or specifications for the active substance	24/04/2008	05/05/2008		
II/0077	Change(s) to the test method(s) and/or specifications for the finished product	24/04/2008	05/05/2008		
IA/0080	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	05/05/2008	n/a		
II/0070	Change(s) to the test method(s) and/or specifications for the finished product	21/02/2008	26/02/2008		
II/0072	Update of sections 4.4 and 4.8 of the SPC to implement the class labelling text on the risk of apnoea following vaccination of very prematurely born infants agreed by the CHMP in July 2007. Update of Summary of Product Characteristics	15/11/2007	20/12/2007	SmPC	Following a review on the risk of apnoea in very premature infants after immunisation the CHMP recommended a class labelling on apnoea for all vaccines in very premature infants. The SPC was updated to include information about the potential risk of apnoea and the need for respiratory monitoring for 48-72h, when the primary immunisation series is administered to very premature infants (born ? 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. Nonetheless, preterm infants should not be withdrawn from the immunisation scheme because the benefit of vaccination outweighs the risk of apnoea.
II/0068	Change(s) to the manufacturing process for the active substance	15/11/2007	21/11/2007		

IA/0069	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	28/08/2007	n/a	Annex II	
II/0066	Change(s) to the manufacturing process for the finished product	21/06/2007	23/07/2007		
IA/0067	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	19/07/2007	n/a		
II/0060	Change(s) to the test method(s) and/or specifications for the active substance	26/04/2007	10/05/2007		
II/0062	To update section 4.4 of the SPC to add a warning related to immunisation in infants or children with severe neurological disorders. The PL was updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/02/2007	03/05/2007	SmPC, Labelling and PL	Further to a review of the literature, the warning section was updated to reinforce that as for any vaccination, the risk-benefit of administering Infanrix Hexa should be weighed carefully if the infant or child have a severe neurological disorder.
II/0058	Change(s) to the manufacturing process for the active substance	22/02/2007	13/04/2007	SmPC, Labelling and PL	
II/0064	Update of or change(s) to the pharmaceutical documentation	22/02/2007	26/02/2007		
II/0059	Update of or change(s) to the pharmaceutical documentation	22/02/2007	26/02/2007		
II/0063	Change(s) to container	14/12/2006	19/12/2006		

II/0061	Change(s) to the manufacturing process for the finished product	16/11/2006	21/11/2006		
II/0055	Change(s) to the manufacturing process for the active substance	21/09/2006	26/09/2006		
II/0057	Change(s) to the test method(s) and/or specifications for the finished product	27/07/2006	01/08/2006		
II/0044	Change(s) to shelf-life or storage conditions	23/02/2006	07/03/2006		
X/0043	X_01_vi_Qualitative change in declared active substance - Other	23/06/2005	24/01/2006		
II/0051	Change(s) to the manufacturing process for the active substance	14/12/2005	21/12/2005		
II/0049	Change(s) to the manufacturing process for the active substance	14/12/2005	21/12/2005		
R/0048	Renewal of the marketing authorisation.	13/10/2005	17/11/2005	SmPC, Labelling and PL	
II/0047	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		
IB/0053	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	28/09/2005	n/a		

II/0046	Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	13/09/2005	SmPC and PL	
IA/0054	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	05/09/2005	n/a		
IA/0052	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	31/08/2005	n/a		
IA/0050	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	01/08/2005	n/a		
II/0041	Change(s) to the manufacturing process for the active substance	23/06/2005	30/06/2005		
IA/0045	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/04/2005	n/a		
II/0042	Change(s) to container	16/03/2005	23/03/2005		
II/0037	Change(s) to shelf-life or storage conditions	17/02/2005	22/02/2005		
IB/0040	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	02/12/2004	n/a		
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/10/2004	n/a	Labelling and PL	
II/0034	Quality changes	22/04/2004	10/05/2004		
IA/0035	IA_05_Change in the name and/or address of a	12/03/2004	n/a		

	manufacturer of the finished product				
II/0033	Change(s) to the manufacturing process for the active substance	26/02/2004	01/03/2004		
II/0031	Update of Summary of Product Characteristics and Package Leaflet	22/10/2003	27/01/2004	SmPC and PL	
II/0030	Update of section 4.2 of the SPC to include a mandatory booster dose of Hib vaccine. Section 5.1 was amended accordingly. Update of Summary of Product Characteristics	22/10/2003	27/01/2004	SmPC	Based on the submitted data, the CHMP agreed that the MAH should update section 4.2 (Posology and method of administration) to include a booster dose in order to ensure optimal protection against invasive HIB disease. Section 5.1 (Pharmacodynamic properties) was amended accordingly.
IB/0032	IB_23_a_Change in source of excip./reagent to veg./synthetic material - biological act. subst.	03/12/2003	n/a		
II/0026	Change(s) to the test method(s) and/or specifications for the finished product	20/11/2003	24/11/2003		
I/0027	12_Minor change of manufacturing process of the active substance	25/09/2003	03/10/2003		
I/0028	24_Change in test procedure of active substance	19/09/2003	23/09/2003		
I/0025	25_Change in test procedures of the medicinal product	13/08/2003	18/09/2003		
II/0023	Update of sections 4.4, 4.5 and 4.8 of the SPC with regard to concomitant administration of Prevenar, and the possible occurrence of a higher rate of febrile	22/05/2003	07/08/2003	SmPC	Based on the submitted data, the CHMP concluded that the physicians must be informed that when co-administration with Prevenar is given at the same visit the incidence of

	reactions with the co-administration of these vaccines. Update of Summary of Product Characteristics				low-grade fever is increased compared to giving one of the products alone. Therefore, a warning on a possible higher incidence of fever was included under section 4.4 (Special Warnings and Special Precautions for Use), and sections 4.5 (Interaction with other medicinal products and other forms of interaction) and 4.8 (Undesirable effects) were updated accordingly.
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/07/2003	01/08/2003	Labelling and PL	
I/0024	25_Change in test procedures of the medicinal product	26/06/2003	03/07/2003		
I/0022	13_Batch size of active substance	19/02/2003	27/03/2003		
II/0020	Change(s) to the test method(s) and/or specifications for the active substance	20/02/2003	10/03/2003		
I/0021	12_Minor change of manufacturing process of the active substance	20/02/2003	10/03/2003		
II/0018	Quality: Change(s) to the test method(s) and/or specifications for the finished product Quality: 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	17/10/2002	30/10/2002		

II/0017	Update of Summary of Product Characteristics and Package Leaflet	25/07/2002	24/10/2002	SmPC and PL	
I/0019	31_Change in container shape	20/09/2002	27/09/2002		
II/0016	Change(s) to the test method(s) and/or specifications for the finished product	30/05/2002	07/06/2002		
I/0014	30_Change in pack size for a medicinal product	07/11/2001	06/02/2002	SmPC and Labelling	
I/0013	30_Change in pack size for a medicinal product	07/11/2001	06/02/2002	SmPC and Labelling	
I/0012	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	19/12/2001	SmPC, Annex II, Labelling and PL	
I/0015	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	28/11/2001		
I/0011	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	28/11/2001		
II/0003	Update of or change(s) to the pharmaceutical documentation	15/11/2001	27/11/2001		
II/0010	Quality changes	20/09/2001	02/10/2001		
II/0009	Change(s) to the test method(s) and/or specifications for the active substance	23/08/2001	24/09/2001		

I/0008	20_Extension of shelf-life as foreseen at time of authorisation	14/06/2001	18/07/2001		
I/0005	26_Changes to comply with supplements to pharmacopoeias	23/03/2001	18/07/2001		
I/0004	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	14/03/2001	18/07/2001		
I/0002	31_Change in container shape	22/01/2001	18/07/2001		
I/0001	13_Batch size of active substance	25/01/2001	18/07/2001		
I/0006	25_Change in test procedures of the medicinal product	26/04/2001	n/a		
I/0007	20_Extension of shelf-life as foreseen at time of authorisation	26/03/2001	n/a	SmPC	