Synflorix

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
IB/0123	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	25/10/2017	n/a		
II/0117	Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to reflect the results from study10PN-PD-DIT-072, a phase III, open, controlled, multi-centric study to evaluate the immunogenicity, safety and reactogenicity of Synflorix in children at an increased	12/10/2017		SmPC and PL	Based on the submitted data, the SmPC was updated to state that the immunogenicity and safety of Synflorix were assessed in a limited number of primed or unprimed subjects with congenital or acquired asplenia, splenic dysfunction or complement deficiencies: 6 subjects 2-5

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

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	risk of pneumococcal infection. The Package Leaflet is updated accordingly. An updated RMP version 16 has also been submitted. This submission fulfils the post-authorisation measure MEA 065. In addition, the Marketing authorisation holder (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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				years of age and 40 subjects 6-17 years of age (Synflorix is indicated up to 5 years of age). Synflorix was shown to be immunogenic and no new safety concerns were observed in this study. In individuals with splenic dysfunction, a 3-dose schedule of Synflorix should be given as primary vaccination in infants starting vaccination before 6 months of age.
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		
IB/0119/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation	29/08/2017	n/a		

	B.I.e.3.z - Deletion of an approved change management protocol related to AS - Other variation				
IB/0121/G	This was an application for a group of variations. 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	10/08/2017	n/a		
IB/0120	B.I.b.z - Change in control of the AS - Other variation	17/07/2017	n/a		
PSUSA/9262/201612	Periodic Safety Update EU Single assessment - pneumococcal polysaccharide conjugate vaccine (adsorbed) - 10 valent	06/07/2017	n/a		PRAC Recommendation - maintenance
II/0116/G	This was an application for a group of variations. B.II.a.3.b.3 - Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological product B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a	22/06/2017	03/10/2017	SmPC, Labelling and PL	

	new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products 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				
IB/0118	B.II.z - Quality change - Finished product - Other variation	07/06/2017	n/a		
II/0108	Update of sections 4.2 4.4, 4.8 and 5.1 of the SmPC in order to add information obtained from two clinical studies in subjects at risk for pneumococcal infections (study 10PN-PD-DIT-034 and study 10PN-PD-DIT-064). The package leaflet was amended accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make consequential	26/01/2017	03/10/2017	SmPC and PL	Study 10PN-PD-DIT-034 assessed the safety and immunogenicity of Synflorix in children with increased risk for pneumococcal infections, i.e. Human Immunodeficiency Virus (HIV) infected or HIV exposed uninfected infants while study 10PN-PD-DIT-064 assessed the safety and immunogenicity of Synflorix in children with increased risk for pneumococcal infections, i.e. children with sickle cell disease (SCD).

	changes to the RMP and to change the final due date of a post-marketing surveillance study. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Information including immunogenicity and safety results from both studies was added to the product information. The safety profile of Synflorix was considered acceptable in the studied high risk paediatric populations, suggesting that the benefit-risk profile of Synflorix is favourable in these populations. The benefit-risk profile of Synflorix is also considered favourable when administered in a 2+1 schedule beginning at 6 weeks of age. Administration of a booster dose (third or fourth dose) at 9 months of age does not adversely impact the safety profile and could provide additional benefit in terms of increased and prolonged protection. The CHMP considered the proposed changes to the SmPC to be acceptable with some modifications.
IA/0114	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/01/2017	n/a		
II/0110	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	17/11/2016	n/a		
IG/0721	A.7 - Administrative change - Deletion of manufacturing sites	10/10/2016	n/a		
IA/0112	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	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 B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	21/09/2016	n/a		
IB/0109	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	02/09/2016	03/10/2017	SmPC	
IB/0107	B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	26/07/2016	n/a		

PSUSA/9262/201512	Periodic Safety Update EU Single assessment - pneumococcal polysaccharide conjugate vaccine (adsorbed) - 10 valent	07/07/2016	n/a		PRAC Recommendation - maintenance
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		
IB/0105/G	This was an application for a group of variations. 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.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	11/05/2016	n/a		
IA/0104	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	23/03/2016	n/a		

II/0100	B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	10/12/2015	02/05/2016	SmPC, Annex II and Labelling	
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2015	02/05/2016	PL	
II/0099	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	22/10/2015	n/a		
IB/0101/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/10/2015	n/a		
II/0098	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
WS/0748	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	30/07/2015	n/a		

	starting material/reagent/intermediate - Other variation				
II/0096/G	This was an application for a group of variations. Update of section 5.1 of the SmPC with effectiveness data against pneumococcal vaccine serotypes and against vaccine related serotype 19A, and update of section 4.4 of the SmPC to include information on the immune response against serotype 19A observed in infants and children. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC, and to request extensions to the due dates for MEA 009: Study 10PN-PD-DIT-034 (111634) and MEA 018.5: Study 10PN-PD-DIT-064 (114056). A revised RMP version 13 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/07/2015	02/05/2016	SmPC	In Brazil, Synflorix was introduced into the national immunization programme (NIP) using a 3+1 schedule in infants (2, 4, 6 months of age and a booster dose at 12 months) with a catch-up campaign in children up to 2 years of age. Based on almost 3 years of surveillance following Synflorix introduction, a matched case-control study reported a significant decrease in culture or PCR confirmed IPD due to any vaccine serotype, and IPD due to individual serotypes 6B, 14 and 19A. In Finland, Synflorix was introduced into NIP with a 2+1 schedule in infants (3, 5 months of age and a booster dose at 12 months) without catch-up campaign. Before and after NIP comparison suggests a significant decrease in the incidence of any culture confirmed IPD, any vaccine serotype IPD and IPD due to serotype 19A. It has also been demonstrated that Synflorix induces an immune response to the cross-reactive serotype 19A with 48.8% (95% CI: 42.9;54.7) of vaccinees reaching an OPA titre ☐ 8 one month after a booster dose.
PSUSA/9262/ 201412	Periodic Safety Update EU Single assessment - pneumococcal polysaccharide conjugate vaccine (adsorbed) - 10 valent	11/06/2015	n/a		PRAC Recommendation - maintenance

II/0092	Update of section 4.4 of the SmPC and corresponding section of the Package Leaflet with the information on effects of paracetamol and ibuprofen used prophylactically on fever and immune responses following primary vaccination and a booster dose of Synflorix. This submission fulfils the obligations with regards to Article 46 of Regulation (EC) No 1901/2006. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015	02/05/2016	SmPC and PL	Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. Clinical data generated with ibuprofen suggest that its delayed use might reduce fever, while prophylactic use of ibuprofen showed a limited effect. Furthermore, the clinical data generated with paracetamol suggest that it might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known.
IB/0094/G	This was an application for a group of variations. B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line) B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line) 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	17/02/2015	n/a		
IB/0093/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	23/12/2014	n/a		

	re-test period/storage period supported by real time data 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				
IB/0091/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	23/12/2014	n/a		
IB/0089	To delete a non-significant in-process test limit (the upper limit of the diphtheria toxoid content range) at the end of two ultrafiltration steps in the purification process of the Diphteria Toxoid for the production site in Gödöllő, Hungary. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	17/12/2014	n/a		
IB/0088	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	12/12/2014	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
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. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/11/2014	n/a		
II/0078	Update of section 4.2 of the SmPC to delete the information related to a booster dose for children 12-23 months of age. Sections 4.4 and 5.1 are also	25/09/2014	27/10/2014	SmPC	Based on the available data, the posology for unvaccinated infants and children ≥ 7 months of age and the related warning were updated as follows:

	updated following the results of new paediatric data related to unvaccinated infants and children ≥ 7 months of age. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				- Section 4.2: for unvaccinated infants and children ≥ 7 months of age, children aged 12 months - 5 years: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses. - Section 4.4: Children younger than 2 years old should receive the appropriate-for-age Synflorix vaccination series (see section 4.2). The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines in children ≥ 2 years of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness, or those who are immunocompromised) placing them at higher risk for invasive disease due to Streptococcus pneumoniae. Whenever recommended, children at risk who are ≥ 24 months of age and already primed with Synflorix should receive 23-valent pneumococcal polysaccharide vaccine. In addition, the new paediatric data related to this population were also reflected in section 5.1 of the SmPC.
II/0083	Submission of a re-analysis of convulsions and swelling reactions reported following vaccination with Synflorix. As a consequence, an updated version of the Synflorix RMP (version 11.0) was submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		The MAH comprehensively re-analysed the convulsions and swelling reactions reported following vaccination with Synflorix. The CHMP concluded that that the results of the updated review are in line with the information already reflected in Product Information.
II/0082	Submission of the final study report of study 10PN-PD-DIT-041 Y4, designed to evaluate the long term persistence of antibody, approximately 48 months post-booster, in children who either received 4 doses	25/09/2014	n/a		The results of this study confirm the information already reflected in the Summary of Product Characteristics (SmPC). Persistence and immunological memory data have already been assessed, and are presented in the Product

	of Synflorix or Prevenar or children who received 3 primary doses of Prevenar and a booster dose of Synflorix. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				Information and the safety results were in agreement with what is previously known regarding the safety profile of Synflorix. It was, therefore, not considered necessary to update the Product Information.
II/0079	Update of section 5.1 of the SmPC to reflect the results of the phase III/IV clinical trial FinIP (Finnish Invasive Pneumococcal disease vaccine) to evaluate the effectiveness of Synflorix (against reduction of hospital-diagnosed pneumonia and impact on tympanostomy tube placements) to address a post-authorisation measure in the Risk Management Plan. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	27/10/2014	SmPC	In the Finnish Invasive Pneumococcal disease vaccine study, the vaccine effectiveness in reducing hospital-diagnosed pneumonia cases (identified based on the International Classification of Diseases, ICD 10 codes for pneumonia) was 26.7% (95% CI: 4.9; 43.5) in the 3+1 infant schedule and 29.3% (95% CI: 7.5; 46.3) in the 2+1 infant schedule. For catch-up vaccination, vaccine effectiveness was 33.2% (95% CI: 3.0; 53.4) in the 7-11 month cohort and 22.4% (95% CI: -8.7; 44.8) in the 12-18 month cohort. Therefore, the results are similar between the different vaccination schedules and show the effectiveness of the vaccine in reducing hospital-diagnosed pneumonia cases. This study did not show significant results for the effectiveness of tympanostomy tube replacement.
IB/0085	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	27/08/2014	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	20/08/2014	n/a		

	parameter)				
II/0075	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	24/07/2014	27/10/2014	SmPC and PL	
PSUV/0077	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
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		
IB/0080	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	21/05/2014	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/0445/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/03/2014	n/a		

	-Additional manufacturer of finished product. -Additional quality control testing manufacturer of the product. -Scale up of active substance of vaccine. -Introduction of alternative containers for the active substance. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs				
R/0068	Renewal of the marketing authorisation.	18/12/2013	21/02/2014	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Synflorix remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

					• Identified risks including febrile convulsions, apnoea in premature infants, and hypotonic hyporesponsive episode (HHE) were observed with increasing rates. Emerging safety concerns, such as Kawasaki disease need further follow-up. • Potential serotype replacement. Therefore, based upon the safety profile of Synflorix, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0069	Update of sections 4.4 and 5.1 of the SmPC with invasive pneumococcal disease (IPD) efficacy data, acute otitis media (AOM) efficacy data and carriage impact data coming from 2 large Phase III clinical studies. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/02/2014	27/10/2014	SmPC	The MAH has presented new data regarding invasive pneumococcal disease (IPD), acute otitis media (AOM) and nasopharyngeal carriage from the COMPAS and the Finnish study 053. The data are considered relevant to include in the SmPC. The studies have partly been presented in other procedures e.g. variations applications EMEA/H/C/000973/II/0052 and II/0070, but the current evaluation was focussed on the data relevant to the proposed updates of the SmPC. In conclusion the IPD data from the COMPAS study support the previously presented data. The protective efficacy/effectiveness against AOM in the COMPAS and 053 studies was lower than expected. Updated analyses of the studies were provided. The results for the catch-up vaccination schedules did not change substantially, but as discussed by the MAH, are not considered robust, especially due to the short follow-up period. The study was not designed to compare different vaccination schedules, and the confidence intervals are generally wide for the AOM endpoints. Therefore the results should not be presented in detail; however a brief summary should be included in the

					SmPC. The CHMP considered that risk benefit balance of Synflorix remains favourable in the approved indication.
II/0070	Update of section 4.8 of the SmPC to revise the safety information upon a safety pooled analysis from primary vaccination, booster and catch-up studies. The Package Leaflet was updated in accordance. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/01/2014	27/10/2014	SmPC and PL	This variation summarizes the safety and reactogenicity data for Synflorix up to the data lock point (DLP) of December 10, 2012 and thus accounts for clinical studies completed since the first licensure of Synflorix in December 11, 2008. The safety data from these clinical studies has significantly increased the safety database for Synflorix. The safety review supported the revisions of section 4.8 of the SmPC. The numbers of subjects exposed to Synflorix and the number of doses received in clinical trials was updated. In addition, the percentages of the most common local adverse reaction after primary vaccination observed in clinical trials was revised as well as the frequencies for crying abnormal, rash and urticaria. The revisions of section 4.8 of the SmPC do not affect the overall positive benefit / risk profile of Synflorix.
II/0052	Extension of indication to include active immunisation against pneumonia for Synflorix. As a consequence, sections 4.1, 4.4 and 5.1 of the Summary of Product Characteristics have been updated with data from study10PN-PD-DIT-028 - Clinical Otitis Media and Pneumonia Study (COMPAS). The Package Leaflet was updated in accordance. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) -	24/10/2013	25/11/2013	SmPC, Labelling and PL	Please refer to Assessment Report EMEA/H/C/000973/II/52.

	Addition of a new therapeutic indication or modification of an approved one				
II/0071	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/09/2013	25/11/2013	SmPC and PL	
IA/0072/G	This was an application for a group of variations. 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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	15/08/2013	n/a		
IB/0065/G	This was an application for a group of variations. 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	18/07/2013	n/a		

	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 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 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 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 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 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				
IA/0067/G	This was an application for a group of variations. 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	03/07/2013	n/a		

	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 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 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 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/0383	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes on the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the	27/06/2013	n/a		

	manufacture of a biological/immunological medicinal product and is not related to a protocol				
II/0057	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	27/06/2013	25/11/2013	SmPC, Labelling and PL	
IG/0306	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2013	n/a		
IB/0063	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	06/06/2013	n/a		
II/0051	Update of section 4.8 of the SmPC in order to update the safety information. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	25/11/2013	SmPC, Labelling and PL	This variation application provided safety and reactogenicity data for Synflorix up to the data lock point (DLP) of December 10, 2011. The safety database for Synflorix from clinical studies completed up to the DLP, consisted of 18 primary vaccination studies (including 7166 subjects in Total vaccinated cohort primed with Synflorix), 15 completed booster studies (5848 subjects in Booster Total vaccinated cohort receiving Synflorix) and five catch-up studies (883 subjects in Catch-up Total vaccinated cohort receiving Synflorix). In addition, post-marketing surveillance data in MAH worldwide safety database up to the DLP of April 2012 has been reviewed for spontaneous reports related to anaphylaxis and angioedema. Changes to the SmPC dealing with local and systemic events noted in primary, booster and catch up vaccination studies were proposed. The proposed additions/revisions to

					the SmPC were endorsed by the CHMP. The CHMP considered there was sufficient evidence of a causal relationship between Synflorix administration for anaphylaxis and angioedema to warrant an update of the relevant sections of the Product Information. Overall, the studies conducted with Synflorix and the post-marketing surveillance have demonstrated that the vaccine can be safely administered to infants and children up to 5 years of age together with other routinely administered paediatric vaccines.
IG/0304	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	17/05/2013	25/11/2013	Annex II	
IG/0297	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2013	n/a		
IB/0060	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	17/04/2013	n/a		
IB/0058	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	05/02/2013	n/a		
IG/0265/G	This was an application for a group of variations.	28/01/2013	n/a		

	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				
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		
IB/0056	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	04/01/2013	n/a		
IB/0055	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change	12/12/2012	n/a		

	management protocol - Implementation of a change for a biological/immunological medicinal product				
IB/0054	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	19/11/2012	n/a		
II/0044	Update of section 4.4 of the SmPC to add a warning related to psychogenic syncope. The package leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	25/10/2012	SmPC and PL	The MAH provided a safety review to support an insertion of a warning statement regarding syncope associated with the injection of Synflorix. There has only been one possible report out of 63 million doses of Synflorix administered world-wide. The vast majority of doses were given to younger children, but some increase in the use in older children could be expected, as catch-up programs are introduced. It is therefore highly unlikely that insertion of a warning will prevent any further injuries among the infants, but possibly among the older children. In conclusion, the CHMP considered the inclusion of a warning in section 4.4 acceptable with the specification of the age range when these reactions could be expected. The update of contact details of local representatives was accepted.
IB/0050	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	26/09/2012	n/a		
IB/0048	B.V.c.1.c - Change management protocol - Update of	12/09/2012	n/a		

	the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product				
IA/0049/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	06/09/2012	25/10/2012	SmPC and Labelling	
IB/0047	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	06/07/2012	n/a		
IB/0046	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	12/06/2012	n/a		
IB/0045	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	29/05/2012	n/a		
WS/0239	This was an application for a variation following a worksharing procedure according to Article 20 of	19/04/2012	n/a		

	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 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				
WS/0237/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. additional facility for drug product manufacture and QC testing 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	19/04/2012	n/a		

II/0040/G	This was an application for a group of variations. Addition of a manufacturing site for the finished product. Change in immediate packaging of the finished product. Addition of a site where testing take place. 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.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and 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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/03/2012	15/03/2012		
IB/0041	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	06/03/2012	n/a		
II/0029	Update of section 4.8 of the SmPC in order to update the safety information [addition of hypotonic-hyporesponsive episode in the undesirable effects	15/12/2011	31/01/2012	SmPC, Annex II, Labelling	The cumulative review of cases of hypotonic hyporesponsive episode from clinical trial setting as well as from post-marketing experienced provided sufficient

	Table]. The PL and Labelling are updated in accordance. In addition, the MAH took the opportunity to include information on paediatric development in section 5.1 of the SmPC, to make minor corrections to the SmPC in line with QRD template and to update Annex II in line with current CHMP recommendations. The list of local representatives in the PL was also updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			and PL	evidence of a potential causal association between Synflorix administration and HHE. This review supports the addition of hypotonic hyporesponsive episode to the table included in 4.8 of the SmPC.
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	19/01/2012	n/a		

	product - Minor changes to an approved test 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/0025	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 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	20/10/2011	20/10/2011		

IA/0028	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/09/2011	n/a		
IB/0027	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	10/08/2011	n/a		
II/0020	Update of Summary of Product Characteristics, Annex II and Package Leaflet The scope of the variation includes updating the indication Section 4.1 to increase the upper age limit of infants and children from 2 years to 5 years and updating all relevant sections of the Summary of Product Characteristics (SmPC), i.e. 4.1, 4.2, 4.8 and 5.1,Annex II and Package Leaflet. Addition of a new therapeutic indication or Modification of an approved one to increase the upper age limit to 5 years. Amend the version number of the RMP mentioned in Annex II in order to reflect the latest approved RMP version 5.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/06/2011	05/08/2011	SmPC, Annex II and PL	Pease refer to the Assessmenr Report for variation II/20.
IB/0026	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	18/07/2011	n/a		

	of the AS				
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		
II/0024/G	This was an application for a group of variations. To add a new manufacturing site for the finished product and to introduce some changes in the manufacturing process of the finished product. 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.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 B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products	19/05/2011	29/06/2011	SmPC, Labelling and PL	
II/0023	Post-approval change management protocol for the addition of a new manyfacturing site for the intermediates and active substances. B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the	19/05/2011	19/05/2011		

	AS				
IG/0064/G	This was an application for a group of variations. Update of section 4.8 of the SmPC to include immediate injection site pain, stinging and burning sensation. The PL is updated in accordance. The MAH has also taken the opportunity to align section 4.6 of the prefilled syringe presentation with the vial presentation. Furthermore, the Labelling is updated to specify the container 'prefilled syringe'. In addition, the MAH has taken the opportunity to update the list of local representatives in the PL. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters 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	04/05/2011	n/a		Following clusters of spontaneous reports of immediate onset injection site pain reported in certain batches of the preservative-free formulation of Twinrix Adult, immediate pain, stinging and burning at the injection site has been reflected in section 4.8 of the SmPC and section 4 of the package leaflet. The MAH's investigation report revealed no specific root cause for the clusters of reports of immediate injection site pain. The injection site reactions were non-serious and self-limited in all cases. The benefit-risk of Twinrix Adult remains positive.

	the product information B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
IG/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	Annex II	
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	18/03/2011	n/a		

	parameter)				
II/0021	Post-approval change management protocol for the addition of a Quality Control activities site B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	17/02/2011	04/03/2011		
II/0016	The MAH seeks to update section 4.2, 4.8 and 5.1 of the SmPC to include information on preterm infants based on the data provided in response to FUM 005 and FUM 006 that have been assessed by the Rapporteur and reviewed by the CHMP. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	24/01/2011	SmPC and PL	The current SmPC of 10Pn-PD-DiT in Europe has no recommendation with respect to the posology for vaccination of preterm infants and no description of the immunogenicity and safety of vaccination in preterm infants. The MAH has received requests from immunisation experts and healthcare professionals from several European Member States to have clarification of vaccination status for preterm infants and inclusion of the data in the SmPC for 10Pn-PD-DiT. The update of SmPC section 4.2, 4.8 and 5.1 of the SmPC to include information on preterm infants is based on data of two studies (primary and booster studies) that evaluate the safety, reactogenicity and immunogenicity of 10Pn-PD-DiT when co-administered with DTPa-HBV-IPV/Hib vaccine in preterm infants (born after a gestation period of 27-36 weeks) as a 3-dose primary immunisation course during the first 6 months of life and then a booster dose at the age of 16-18 months (Studies 10PN-PD-DIT-015 and 10PN-PD-DIT-016). Having assessed these data the CHMP supports the inclusion of information on preterm infants in the SmPC

					(sections 4.2, 4.8 and 5.1) to give clear guidance to prescribers how to use the 10Pn-PD-DiT vaccine in this vulnerable group.
II/0014	Update of section 4.2 of the SmPC with a recommendation for use of Synflorix with 2+1 schedule in routine infant immunisation programmes and to add paragraphs in section 5.1 to reflect immunogenicity data on the 2-dose primary vaccination schedule. The immunogenicity of Synflorix following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in studies 10PN-PD-DIT-002 and -011. The recent study 10PN-PD-DIT-046 assessed the persistence and immunological memory following 2+1 and 3+1 vaccination. Amendment to section 4.4 with a statement that vaccination in high risk groups should be considered on an individual basis, with a cross-reference to section 4.2. To ensure the safe and proper administration of Synflorix using a pre-filled syringe, the MAH took the opportunity to update section 6.6 of the SmPC to include further instructions for the use of the pre-filled syringe (with illustration). Some further minor amendments have been made in the SmPC to comply with the latest version of the QRD template.	16/12/2010	24/01/2011	SmPC and PL	The immunogenicity of Synflorix following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in studies 10PN-PD-DIT-002 and -011. The recent study 10PN-PD-DIT-046 assessed the persistence and immunological memory following 2+1 and 3+1 vaccination. The product information has been updated accordingly.

	Finally the details of the MAH's local representatives in EU countries have been updated in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IB/0019	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/01/2011	n/a		
II/0015	Changes to a test procedure for polysaccaride content for the finished product release. B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	16/12/2010	12/01/2011		
IB/0022	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/01/2011	n/a		
IB/0018	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	07/01/2011	n/a		
IB/0013	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	28/06/2010	n/a		

	specification parameter to the specification with its corresponding test method				
WS/0001	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To register an additional building for formulation activities. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.	22/04/2010	22/04/2010		
II/0011	Changes to the manufacturing process of the drug substance Change(s) to the manufacturing process for the active substance	18/02/2010	03/03/2010		
II/0010	Changes to manufacture and control of the drug susbtance Change(s) to the manufacturing process for the active substance	18/02/2010	03/03/2010		
II/0009	Changes of shelf life Change(s) to shelf-life or storage conditions	18/02/2010	03/03/2010		

II/0006	Changes to the specifications for the active substance Change(s) to the test method(s) and/or specifications for the active substance	18/02/2010	03/03/2010		
IB/0012	B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	26/02/2010	n/a		
II/0007	Change to the control of the drug product Change(s) to the test method(s) and/or specifications for the finished product	19/11/2009	19/11/2009		
IA/0005	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	31/07/2009	n/a		
II/0003	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	13/07/2009		
II/0004	Optional release program intended for National Control Laboratories in International countries that require independent laboratory testing for lot release purpose of Synflorix drug product. Change(s) to the test method(s) and/or specifications for the finished product	29/05/2009	08/06/2009		

IB/0001	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	07/05/2009	07/05/2009	SmPC, Labelling and PL	
IA/0002	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	17/04/2009	n/a		