EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Infanrix penta

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/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		

[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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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/0299	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	26/04/2013	n/a		

IG/0297	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2013	n/a		
II/0086	Replacement of the current screwcaps used for the purified bulk transfer and storage. B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs	21/02/2013	n/a		
WS/0336	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To introduce a new method for monitoring homogeneity during filling. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	17/01/2013	n/a		
WS/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/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 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	19/04/2012	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	19/01/2012	n/a		

	product - Minor changes to an approved test procedure				
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		
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 sensation. The PL is updated in accordance. The MAH	04/05/2011	n/a		Following clusters of spontaneous reports of immediate onset injection site pain reported in certain batches of the preservative-free formulation of Twinrix Adult, immediate pain, stinging and burning at the injection site has been reflected in section 4.8 of the SmPC and section 4 of the

	has also taken the opportunity to align section 4.6 of the prefilled syringe presentation with the vial presentation. Furthermore, the Labelling is updated to specify the container 'prefilled syringe'. In addition, the MAH has taken the opportunity to update the list of local representatives in the PL. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				package leaflet. The MAH's investigation report revealed no specific root cause for the clusters of reports of immediate injection site pain. The injection site reactions were non-serious and self-limited in all cases. The benefit-risk of Twinrix Adult remains positive.
IG/0052/G	This was an application for a group of variations. B.II.e.2.a - Change in the specification parameters	18/03/2011	n/a		

	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)				
II/0072	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/0068	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/0067	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 penta continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of

					Infanrix penta 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 and Cyprus.
IB/0069	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		
IB/0071	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		
IA/0070	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		
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.	22/04/2010	22/04/2010		

	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.				
II/0066	Change in cell identity method. Change to the test procedure and/or specification of a raw material	17/12/2009	08/01/2010		
IB/0065	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	18/09/2009	n/a		
IB/0064	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	20/07/2009	n/a		
II/0062	Introduction of new filter equipment during the manufacturing process of tetanus toxoid. Change(s) to the test method(s) and/or specifications for the active substance	25/06/2009	06/07/2009		
II/0063	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/0057	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/0058	Modification of the purification process for tetanus toxoid. Change(s) to the manufacturing process for the active substance	19/03/2009	24/03/2009		
II/0059	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/0060	IB_20_c_Change in test procedure for an excipient - other changes	11/02/2009	n/a		
IA/0061	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/02/2009	n/a		
IB/0056	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	23/12/2008	n/a		
IA/0055	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	18/11/2008	n/a		
II/0049	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 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	25/09/2008	30/10/2008	SmPC, Annex II, Labelling and PL	Based on data from clinical trials and post marketing setting the product information was updated in order to clarify the prescribing information and extend the advice provided to the health care provider. 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. Apnoea was added as reported in the post marketing setting, in line with

	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				the warning which had been added following a variation that affected all infant vaccines. 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. Wording on persistence of protective antibodies against Hepatitis B was included in the product information. 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/0050	Update of section 5.1 of the SPC with information from a pertussis vaccine surveillance and effectiveness study in Sweden. The MAH also took the opportunity to update the contact details of a local representative in the PL. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	13/08/2008	SmPC and PL	The effectiveness of several acellular pertussis-based combined vaccines was assessed via a long-term surveillance study in Sweden. Results over eight years of 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/0051	Update of section 4.2 of the SPC to harmonise the information on booster vaccination with that of Infanrix hexa. The PL was consequentially updated. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	13/08/2008	SmPC and PL	Infanrix penta and Infanrix hexa are both indicated for primary and booster vaccination of infants. The primary vaccination schedule consists of three doses (such as 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) with an interval of at least one month between doses. Alternatively two doses may be administered in a schedule such as 3 and 5 months. Booster vaccination after the three-dose primary schedule should be administered at least 6 months after the last dose in the primary course and preferably before 18 months of

					age. After primary vaccination with two doses a booster dose should be given at least 6 months after the last primary dose and preferably between 11 and 13 months of age. These recommendations have now been clarified in the SPC for Infanrix penta in order to be in line with that of Infanrix hexa.
IA/0054	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/07/2008	n/a		
II/0047	Change(s) to the manufacturing process for the active substance	30/05/2008	05/06/2008		
II/0052	Change(s) to the test method(s) and/or specifications for the finished product	24/04/2008	05/05/2008		
II/0053	Change(s) to the test method(s) and/or specifications for the active substance	24/04/2008	05/05/2008		
II/0048	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	18/12/2007	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/0045	Change(s) to the manufacturing process for the active substance	15/11/2007	21/11/2007		

IA/0046	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	
IA/0044	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	19/07/2007	n/a		
II/0039	Change(s) to the test method(s) and/or specifications for the active substance	26/04/2007	10/05/2007		
II/0041	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 Penta should be weighed carefully if the infant or child have a severe neurological disorder.
II/0038	Change(s) to the manufacturing process for the active substance	22/02/2007	13/04/2007	SmPC, Labelling and PL	
II/0042	Update of or change(s) to the pharmaceutical documentation	22/02/2007	26/02/2007		
II/0040	Change(s) to the manufacturing process for the finished product	16/11/2006	22/11/2006		
X/0028	X_01_vi_Qualitative change in declared active substance - Other	23/06/2005	24/01/2006		
II/0033	Change(s) to the manufacturing process for the active substance	15/12/2005	21/12/2005		

R/0032	Renewal of the marketing authorisation.	13/10/2005	17/11/2005	SmPC, Labelling and PL	
II/0031	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/0035	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	28/09/2005	n/a		
II/0030	Update of section 4.8 of the SPC to include information on limb swelling, following the assessment of the 5th-8th PSURs covering the period from 23 October 2003 to 22 October 2004. Relevant sections of the PL were updated accordingly . Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	13/09/2005	SmPC and PL	In line with the CHMP recommendations further to the assessment of the data from the 5th-8th PSURs, the MAH applied to update the information regarding limb swelling. The new wording provided allows differentiation between the levels of severity of the swelling: ? 50 mm circumference (very common) and > 50 mm circumference (common). Furthermore "swelling of the entire injected limb" was included as observed during post-marketing surveillance".
IA/0036	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	05/09/2005	n/a		
IA/0034	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	31/08/2005	n/a		
II/0027	Change(s) to the manufacturing process for the active substance	23/06/2005	30/06/2005		
IA/0029	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/04/2005	n/a		

N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2004	n/a	Labelling and PL	
IB/0025	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	02/12/2004	n/a		
II/0023	Quality changes	22/04/2004	10/05/2004		
IA/0024	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/03/2004	n/a		
II/0022	Change(s) to the manufacturing process for the active substance	26/02/2004	01/03/2004		
IB/0021	IB_23_a_Change in source of excip./reagent to veg./synthetic material - biological act. subst.	03/12/2003	n/a		
II/0018	Change(s) to the test method(s) and/or specifications for the finished product	20/11/2003	24/11/2003		
I/0019	12_Minor change of manufacturing process of the active substance	25/09/2003	03/10/2003		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/08/2003	16/09/2003	Labelling and PL	
I/0017	25_Change in test procedures of the medicinal product	26/06/2003	03/07/2003		
II/0016	Change(s) to the test method(s) and/or specifications for the active substance	20/02/2003	10/03/2003		
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/09/2002	08/10/2002	PL	

I/0014	31_Change in container shape	20/09/2002	27/09/2002		
II/0013	Change(s) to the test method(s) and/or specifications for the finished product	30/05/2002	07/06/2002		
I/0010	30_Change in pack size for a medicinal product	07/11/2001	06/02/2002	SmPC and Labelling	
I/0011	30_Change in pack size for a medicinal product	07/11/2001	06/02/2002	SmPC and Labelling	
I/0009	03_Change in the name and/or address of the marketing authorisation holder 01_Change following modification(s) of the manufacturing authorisation(s)	05/11/2001	18/12/2001	SmPC, Annex II, Labelling and PL	
I/0008	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	28/11/2001		
I/0012	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	28/11/2001		
II/0002	Update of or change(s) to the pharmaceutical documentation	15/11/2001	27/11/2001		
II/0007	Quality changes	20/09/2001	02/10/2001		
II/0006	Change(s) to the test method(s) and/or specifications for the active substance	23/08/2001	24/09/2001		
I/0004	25_Change in test procedures of the medicinal product	26/04/2001	n/a		
I/0005	20_Extension of shelf-life as foreseen at time of authorisation	26/03/2001	n/a	SmPC	

I/0003	26_Changes to comply with supplements to pharmacopoeias	23/03/2001	n/a		
I/0001	13_Batch size of active substance	25/01/2001	n/a		