Pandemrix

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
II/0079	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	28/04/2016		SmPC, Annex II, Labelling and PL	
II/0078	Submission of the study report for a non-clinical study undertaken in cotton rats to evaluate the potential	21/05/2015	14/12/2015	Annex II	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).

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	impact of Pandemrix vaccination/H1N1v infection on the blood-brain-barrier integrity and CNS inflammation/damage, in order to fulfil one part of the post-authorisation measure ANX 116. Annex II has been updated accordingly. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/2277/ 201409	Periodic Safety Update EU Single assessment - pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted) a/california/7/2009 (h1n1)v like strain (x-179a)	10/04/2015	n/a		PRAC Recommendation - maintenance
II/0077	Update of Annex II to reflect the fulfilment of a condition to the Marketing Authorisation to conduct a retrospective pharmacoepidemiological study in Canada (Quebec) and follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	26/03/2015	14/12/2015	Annex II	The present submission addresses the condition of the Marketing Authorisation (to conduct a retrospective epidemiological study in Canada (Quebec) and follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects), a commitment related to the Québec study of Arepanrix H1N1 and narcolepsy, which is part of the epidemiological research plan agreed by the MAH and CHMP/EMA. With the submission of the final study report on the Quebec study, the mentioned condition of the MArketing Authorisation is considered to be fulfilled and, therefore, Annex II of the Marketing Authorisation has been updated to reflect that this is no longer required.

II/0076	Update of Annex II to reflect the fulfilment of a condition to evaluate the potential immunological differences between Pandemrix (D-Pan-H1N1) and Arepanrix (Q-Pan-H1N1). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	26/03/2015	14/12/2015	Annex II	As part of the Marketing Authorisation condition (to establish a non-clinical research plan consisting of a series of in vitro and in vivo experiments, aimed at understanding the root cause of the association between Pandemrix and narcolepsy induction), the MAH has submitted in this application results of an evaluation of the potential for immunological differences between Pandemrix and Arepanrix H1N1 using antibody avidity analysis and phage display-assisted epitope mapping from clinical serum samples obtained before and at Day 21 after vaccination from clinical studies in which the two vaccines were compared. As a consequence, the CHMP considered that this part of the condition has been fulfilled and the wording of the condition in Annex II has been updated accordingly.
II/0074	Update of obligations to conduct postauthorisation non-clinical studies including timings for key data planned to further elucidate the potential role of Pandemrix in the onset of narcolepsy. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	18/12/2014	14/12/2015	Annex II	
II/0069	To revise the indication to reflect that Pandemrix should only be used for prophylaxis of influenza caused by A(H1N1)v 2009 if recommended seasonal influenza vaccine is not available and immunisation against A(H1N1)v 2009 is considered necessary, to update sections 4.4 and 4.8 of the SmPC to reflect the totality of the data on the risk of narcolepsy and to	26/06/2014	28/07/2014	SmPC, Annex II and PL	Please refer to the scientific discussion Pandemrix EMEA/H/C/000835/II/0069-AR.

	provide an updated benefit-risk assessment of Pandemrix, based on the data currently available to the MAH on H1N1 influenza disease burden, effectiveness and safety of Pandemrix and available epidemiology data on narcolepsy. The Package Leaflet is updated accordingly. The MAH also took the opportunity to update the list of 'Obligation to conduct post-authorisation measures' in Annex II to remove the condition "Re-analysis of the dataset with adjustment for medically-attended respiratory infection/influenza-like illness" as the MAH will not be in a position to fulfil this request. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0072	Submission of the annex report for the solid organ transplant (SOT) rejection study which covers the tertiary objectives related to seasonal trivalent influenza vaccination and SOT rejection in fulfilment of a post authorisation measure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/06/2014	n/a		The MAH already submitted in the context of a type II variation (II-67) the final study report for EPI-FLU-H1N1-012 (Risk of solid organ transplant rejection following vaccination with Pandemrix in the United Kingdom). The second annex report presenting results for the tertiary study objective (whether TIVs were associated with an increased organ rejection risk during influenza seasons between 2006 and 2009) has now been submitted. As discussed in the assessment of the main study results, overall this appears to be a well-conducted study which did not find an association between either Pandemrix or seasonal trivalent influenza vaccine and SOT rejection in the UK CPRD. In this annex report, the majority of the risk point estimates were close to 1 and the upper limits of the estimates appear to exclude around a 3-fold or greater increased risk of SOT rejection one and two months following vaccination.

					Generally, the findings were similar to those presented for Pandemrix in the main report.
II/0068	To provide a review of the data from the test-negative case-control analysis of a retrospective epidemiological study conducted in Quebec, Canada to evaluate the risk of narcolepsy associated with vaccination with Arepanrix and to follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	26/06/2014	28/07/2014	Annex II	These additional test-negative case-control analyses indicate, as with the previous cohort and self controlled case series (SCCS) analysis, that there is a lack of power in the Quebec dataset which is related to the low number of cases identified. The lack of age-stratified analysis due to low numbers of discordant case-control pairs is also unfortunate but unsurprising given the small number of cases identified in Quebec. Similar to the previous cohort and SCCS results, the additional case-control study results from the Quebec narcolepsy dataset appear to allow for a magnitude of narcolepsy risk as seen with Pandemrix in Europe to be excluded. However, based on a combination of study limitations including the lack of power and differing results between the cohort, SCCS and case-control analyses, the existence of a smaller increased risk with Arepanrix used in Canada cannot be ruled out. To this end, the conclusions of the CHMP at the time of considering the previous Quebec study report in March 2013 are largely unchanged.
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		
II/0067	To submit the final report for the SCCS analysis of Pandemrix and solid organ transplant rejection in the GPRD GOLD to conduct a retrospective study in a suitable population of transplant recipients to further evaluate this signal.	22/05/2014	n/a		The MAH has submitted in the context of a type II variation the final study report for EPI-FLU-H1N1-012 (Risk of solid organ transplant (SOT) rejection following vaccination with Pandemrix in the United Kingdom). Overall the CHMP considered that this study was well-conducted. The main analysis has not found an association between Pandemrix

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				and SOT rejection and this is robust across a number of different sensitivity analyses. The majority of the risk point estimates were close to 1 and the upper limits of the estimates appear to exclude a 2.5-fold or greater increased risk of SOT rejection one and two months following vaccination. The CHMP agreed that these data do not require an update of the Product Information.
PSUV/0070	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
IB/0071	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	10/04/2014	28/07/2014	SmPC and PL	
II/0061	To update the obligations related to narcolepsy in Annex II by listing the proposed non-clinical and epidemiological studies planned to further elucidate the role of Pandemrix in the onset of narcolepsy. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2013	14/03/2014	SmPC, Annex II and PL	Please refer to the scientific discussion of the Assessment Report Pandemrix-H-832-II-61-AR.
IG/0306	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2013	n/a		
IG/0297	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2013	n/a		
IB/0064	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/03/2013	14/03/2014	SmPC and PL	Sections 4.4 and 4.8 of the SmPC were updated to implement the revised wording concerning available data on

					narcolepsy as requested by CHMP in November 2012.
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		
II/0060	To replace the H5N1 clinical trial safety data from section 4.8 of the SmPC with a list of undesirable effects and clinical safety data reported with Pandemrix manufactured with H1N1, based on an integrated summary of reactogenicity from all adult D-PAN H1N1 studies. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of obligations to complete post authorisation measures in Annex II to reflect the status of submissions and to update the list of local representatives in the Package Leaflet. Furthermore, the MAH took the opportunity to bring the PI in line with the latest QRD template version 8. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical,	20/09/2012	24/10/2012	SmPC, Annex II, Labelling and PL	No significant new signal of concern has been identified for Pandemrix from the integrated summary of reactogenicity from the D-PAN H1N1 trials. The adult reactogenicity profile for H1N1 does not appear to be significantly different from that of H5N1, however based on the data submitted the PI was further updated to reflect the apparent increase in the frequency of solicited general AEs (fatigue, headache, joint pain, muscle aches, shivering, sweating and fever) observed in the Pandemrix H1N1 clinical trial data for 18-60 year olds after the second dose compared to the first dose. In addition, in section 4.8 the term ecchymosis was moved to the System Organ Class "General disorders and administration site conditions" under post marketing experience as an injection site reaction. Section 4.8 was further updated to separate somnolence associated with narcolepsy from short-term somnolence that has been observed during clinical use of Pandemrix following vaccination. In addition, the CHMP agreed that a causal relationship between injection site reactions and Pandemrix vaccination does exist and the

	clinical or pharmacovigilance data				MAH's proposal to include 'injection site reactions (such as inflammation, mass)' in the post marketing subsection of 4.8 was considered acceptable.
IB/0059/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	03/04/2012	n/a		
WS/0153	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC to include a warning on psychogenic syncope based on the available safety data. The PL was proposed to be updated in accordance. In addition, the company took the opportunity to update the list of local representatives in the PL of Pumarix, Ambirix, Pandemrix, Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals, Prepandrix and Fendrix. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical,	17/11/2011	19/12/2011	SmPC and PL	Based on a review of literature and a search in the global safety database performed by the MAH, the CHMP recommended including a wording on psychogenic syncope to the product information of the MAH injectable vaccines. The literature review showed an incidence peak occurred around the age of 15 years, with females having more than twice the incidence of males. The syncope reports with secondary injuries were reported most frequently in children and adolescents. Given that psychogenic syncope is not a true side effect, it was not considered appropriate to include syncope as an undesirable effect in section 4.8 of the SmPC. However, as such events can result in injury, and may not have occurred in the absence of the vaccination, the CHMP recommended to add a reference to such events in section 4.4 'Warning and Precaution' of the SmPC and in the PL.

	clinical or pharmacovigilance data				
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		
II/0052	Update of Summary of Product Characteristics To update section 5.1 of the SmPC with clinical data generated in the paediatric studies D-Pan-H1N1-009, D-Pan-H1N1-010 and D-Pan-H1N1-023 at the Month 12 timepoint. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	03/11/2011	SmPC	Please refer to the scientific discussion of the Assessment Report Pandemrix-H-832-II-52-AR.
II/0051	To update sections 4.2 and 5.1 of the SmPC with haemagglutination inhibition (HI) antibody persistence results at month 12 after primary vaccination from studies D-Pan-H1N1-007 and D-Pan-H1N1-008, and neutralising antibody response data up to month 6 from study D-Pan-H1N1-008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	18/08/2011	SmPC	Please refer to the scientific discussion of the Assessment Report Pandemrix-H-832-II-51-AR.
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		

A20/0045	Pursuant to Article 20 of Regulation (EC) No 726/2004 of 31 March 2004, the European Commission requested, on 27 August 2010, the opinion of the CHMP on reports of narcolepsy following vaccination with Pandemrix reported mainly in Sweden and Finland. The CHMP was requested to assess the above concern and its impact on the benefit/risk for Pandemrix and to give its opinion on measures necessary to ensure the safe and effective use of Pandemrix, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.	14/04/2010	17/06/2011	SmPC and Annex II	Please refer to the scientific discussion of the Assessment Report Pandemrix-H-832-A20-45-AR.
II/0050	To reflect the additional HI data obtained from study D-Pan H1N1-020 concerning use in combination with seasonal influenza vaccine in section 4.5 of the SmPC. The MAH took also the opportunity to update Annex II concerning the deletion of the DDPS version number as requested by CHMP and to update the version number of the Risk Management Plan. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/03/2011	17/05/2011	SmPC and Annex II	Additional data from a randomised, single-blind study to evaluate the immunogenicity and safety of sequential administration of Fluarix and Pandemrix (H1N1) and vice versa in adults 61 years or above showed that after the second dose of Pandemrix (two doses were given 21 days apart) a lower immune response to Fluarix was observed as compared to subjects who had not previously received Pandemrix. It is therefore preferable that non-adjuvanted seasonal influenza vaccines should be administered before or with the first dose of Pandemrix. The Product Information was updated to reflect this. The safety data from this study was comparable to that seen in other studies conducted in adults and did not raise any concerns.
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	27/04/2011	n/a		

	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				
II/0048	Update of section 5.1 of the SmPC to include neutralizing immune response data for post dose 1 and post dose 2 in the studies Flu D-Pan H1N1-009, FLU D-Pan-H1N1-010 and FLU D-Pan-H1N1-023 covering individuals 6 months to 17 years of age, as well as persistence data (HI and neutralizing response) at Month 6 from study D-Pan-H1N1-023. The MAH also took the opportunity to update Annex II in line with CHMP recommendations. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/02/2011	24/03/2011	SmPC and Annex II	Please refer to the Scientific Discussion Pandemrix-H-832-II-48-AR
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	18/03/2011	n/a		

	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/0046	To update sections 4.2 and 5.1 of the Summary of Product Characteristics to include persistence results and safety follow-up up to 6 months after primary vaccination from studies D-Pan H1N1-007 (adults 18-60) and D-pan H1N1-008 (adults 18-60 and >60).The MAH also took this opportunity to make a minor correction in the patient leaflet (section 4). 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	21/01/2011	SmPC and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-46-AR
IB/0047	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol	19/11/2010	n/a		
II/0044	To introduce a change in the manufacturing process of the finished product. B.II.b.3.e - Change in the manufacturing process of the finished product - Introduction or increase in the overage that is used for the AS	21/10/2010	27/10/2010		
II/0043	Update of SmPC and PL to update sections 4.8 and 5.1 of the SPC to reflect updated safety and immunogenicity results from clinical studies D-PAN-H1N1-010 and D-PAN-H1N1-023 carried out in	22/07/2010	10/09/2010	SmPC, Annex II and PL	The MAH provided for this variation day 42 (D42) safety and haemagglutination inhibition (HI) immunogenicity data from studies D-Pan H1N1-010 and D-Pan H1N1-023. The MAH also updated some of the information previously submitted

	children aged 3 to 17 years. The Package Leaflet is updated accordingly. The MAH further took the opportunity to correct a spelling error in Annex II. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				based on cleaned datasets and analyses. The provided immunogenicity data showed that HI responses in the age group 10-17 years to one or two half adult doses was satisfactory although geometric mean titres (GMTs) and geometric men fold rises (GMFRs) were lower than observed with full adult doses. There was not a clear advantage for one or two half adult doses in terms of safety compared to one or two full adult doses although there was no trend to increased reactogenicity with the second half adult dose as had been observed with the second full adult dose. Overall the CHMP continues to consider that the SmPC recommendation for a single adult dose of Pandemrix from 10 years upwards is supported. In the age group 3-9 years, the new data on the safety and immunogenicity of second full and half adult doses from studies D-Pan H1N1-010 and 023 submitted for this procedure showed a marked increment in HI titre with the second doses in this age group. A between-study comparison also suggests higher GMTs and GMFRs with full vs. half adult doses. However, the same comparison also suggests greater reactogenicity with full vs. half adult doses. Also, the second adult dose was associated with greater reactogenicity than the first dose whereas this difference was not observed with the second vs. first half adult dose. Overall the CHMP continues to consider that the SmPC recommendation for one or two half adult doses of Pandemrix in children aged 3-9 years is supported.
II/0042	Update of Summary of Product Characteristics Update of SPC to update sections 4.8 and 5.1 of the SPC to reflect updated safety and immunogenicity results (post dose 1 and post-dose 2) from a clinical study with Pandemrix in children aged 6 to 35 months (D-PAN-H1N1-009) based on analysis done on a	22/07/2010	10/09/2010	SmPC and PL	Immunogenicity and safety data form a phase II, randomised, open-label, multicentre study to evaluate the safety and immunogenicity of Pandemrix H1N1 following a homologous prime-boost schedule in children aged 6 to 35 months (H1N1-009) confirmed the previously observed immunogenicity and safety profile. The cleaned and updated

	cleaned data base and generated on a larger population. The MAH also took the opportunity to update the List of local representatives in section 6 of 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				data on one and two half adult doses submitted for this procedure do not change any of the messages previously presented in the SmPC and support maintaining the current advice given in sections 4.2 and 4.4. Sections 4.8 and 5.1 of the SPC and the PL were updated to reflect the updated data.
SW/0041	Switch from conditional to full Marketing Authorisation	24/06/2010	12/08/2010	SmPC, Annex II, Labelling and PL	
II/0039	To amend the instructions for mixing and administration of the vaccine in both the Summary of Product Characteristics and 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	20/05/2010	12/08/2010	SmPC and PL	
II/0038	To update sections 4.8 and 5.1 of the SmPC to include data from a clinical Study (D-Pan-H1N1-008) on the immunogenicity and safety after a single or two-dose schedule of Pandemrix in adults aged 18 years and above. The MAH further took the opportunity to update Annex II to reflect the current status of Specific Obligations. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/05/2010	12/08/2010	SmPC and Annex II	The MAH submitted in support of this procedure post dose-2 data from a phase II, randomised, open-label, single centre study to evaluate the safety and immunogenicity of Pandemrix H1N1 following administration of one or two doses to healthy adults aged from the age of 18 years onwards (H1N1-008). As after the first dose of the vaccine, the CHMP criteria for HI responses were met after a second dose, associated with increments in geometric mean titres (GMTs) and seroconversion factors (SCFs) and a small impact on seroprotection rates (SPRs) and SCRs compared to the first dose.

					The post-dose 2 data also showed that responses were maintained in the group that received only a single dose at day 0 (with the exception of one of two subjects aged >80 years who was not seroprotected at day 42). The safety profile of Pandemrix H1N1 showed that the second dose was slightly less reactogenic than the first dose in the trial population. The pattern of age-related reporting rates was maintained. There were no new safety issues raised by these data. These results were reflected in the Product Information. The CHMP further agreed that the data from this study do not indicate a need to change the current dose recommendations for adults, including the elderly.
IA/0040/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV 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	15/04/2010	n/a	Annex II	
II/0033	Update of Summary of Product Characteristics, Annex II and Package Leaflet To update sections 4.4, 4.8 and 5.1 of the Summary of	21/01/2010	08/02/2010	SmPC, Annex II and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-33-AR

	Product Characteristics to add the safety and immunogenicity data in children aged 3-9 years from two clinical studies (H1N1-010, H1N1-023) carried out in children aged from 3 to 17 years. Annex II and the PL are updated accordingly. In addition the MAH took the opportunity to update Annex II with the current status of Specific Obligations. Update of Summary of Product Characteristics and Package Leaflet				
II/0037	To introduce an additional site for the manufacturing of adjuvant component of the vaccine. 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.	27/01/2010	03/02/2010		
II/0036	To introduce an additional site for the manufacturing of adjuvant component of the vaccine. 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	21/01/2010	03/02/2010		
II/0035	To introduce an additional site for the manufacturing of the antigen finished product and to introduce some changes to an existing site responsible for the production of the antigen component finished product.	11/01/2010	13/01/2010		

	Update of or change(s) to the pharmaceutical documentation				
II/0031	To introduce an additional manufacturing site for the production and the sterility testing of the adjuvant finished product. Update of or change(s) to the pharmaceutical documentation	23/12/2009	05/01/2010		
II/0034	To update section 4.5 of the Summary of Product Characteristics and section 2 of the Package Leaflet to reflect post dose 1 immunogenicity and safety data from a phase III, randomised, single-blind study to evaluate the immunogenicity and safety of sequential administration of a licensed seasonal trivalent vaccine and Pandemrix administered in adults 61 years or above (D-PAN-H1N1-020). The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	22/12/2009	SmPC and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-34-AR
II/0032	To update sections 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics to reflect post dose 2 safety and immunogenicity results from a phase III, observer-blind, randomied trial to evaluate the safety and immunogenicity of a two-dose schedule in adults aged 18 to 60 years (D-PAN-H1N1-007). In addition, data from the population of 10-17 year old subjects from study D-PAN-H1N1-010 has been included. The PL is updated accordingly and Annex IIC	17/12/2009	22/12/2009	SmPC, Annex II and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-32-AR

	has been updated to reflect the current status of the Specific Obligations. Update of Summary of Product Characteristics				
II/0030	To introduce two additional manufacturing sites for the production and the sterility testing of the adjuvant finished product. Update of or change(s) to the pharmaceutical documentation	16/12/2009	18/12/2009		
II/0029	To introduce an additional manufacturing site for the production of the antigen component. Update of or change(s) to the pharmaceutical documentation	19/11/2009	09/12/2009		
II/0028	To update sections 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics to reflect new safety and efficacy data post dose 2 (half adult dose) from a study in children aged 6 to 35 months (D-Pan-H1N1-009). Annex II and the Package Leaflet are updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	09/12/2009	SmPC, Annex II and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-28-AR
II/0027	To introduce an additional manufacturing site for the production of the adjuvant and to introduce some additional activities in one existing manufacturing site for the adjuvant component.	19/11/2009	04/12/2009		

	Change(s) to the manufacturing process for the finished product				
II/0026	To update section 4.8 of the SPC and section 4 of the PL to include information on allergic and anaphylactic reactions reported post-marketing following the use of Pandemrix (H1N1). Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	27/11/2009	SmPC and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-26-AR
II/0025	Update of Summary of Product Characteristics, Annex II and Package Leaflet To update section 4.5 of the SPC and section 2 of the PL to reflect immunogenicity results of study 0018 (administration with seasonal influenza vaccine Fluarix) in adults 18-60 years of age and elderly The MAH also took the opportunity to update section 6.6 of the SPC to amend the instructions for handling to handling take account of the potential appearance of coring. The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	27/11/2009	SmPC, Annex II and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-25-AR
II/0024	Update of Summary of Product Characteristics, Annex II and Package Leaflet To update sections 4.2, 4.4, 4.8 and 5.1 of the	19/11/2009	27/11/2009	SmPC, Annex II and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-24-AR

	Summary of Product Characteristics and Annex IIC to reflect newly available results from clinical study D-PAN-H1N1-009 (post dose 1 (half dose) in 6 months-3 years old children). The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				
II/0023	Update of Summary of Product Characteristics, Annex II and Package Leaflet To update sections 4.2, 4.4, 4.8 and 5.1 of the SPC and Annex IIC to reflect newly available results from clinical study D-PAN-H1N1-008 post-dose 1, (adults 18-60 years and above 60 years old). The PL is updated accordingly. The MAH also took the opportunity to amend wording in section 6.6 of the Summary of Product Characteristics and section 6 of the PL to instruct that the vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant. Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	27/11/2009	SmPC, Annex II and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-23-AR
II/0022	To introduce an additional manufacturing site for the production of the adjuvant component. Update of or change(s) to the pharmaceutical documentation	13/11/2009	17/11/2009		

II/0021	To introduce an additional manufacturing site for the production of the adjuvant and to introduce some changes in its testing process. Update of or change(s) to the pharmaceutical documentation	13/11/2009	17/11/2009		
II/0019	Update of Summary of Product Characteristics, AnnexII, Labelling and Package Leaflet To update sections 4.2 and 5.1 of the SPC for Pandemrix H1N1 to reflect newly available results from a clinical study in adults 18-60 years of age (H1N1-007). The MAH took also the opportunity to update the instructions for mixing and administration of the vaccine in the SPC and PL and to amend section 6.5 of the SPC and the Labelling in line with these changes. On the basis of the information provided by the Marketing Authorisation Holder and as set out in the appended variation assessment report, the CHMP considers this variation to be a Type II variation. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/10/2009	11/11/2009	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion: Pandemrix-H-832-II-19-AR
II/0018	To introduce some changes in the manufacturing process of the H1N1 antigen component. Change(s) to the manufacturing process for the active substance	22/10/2009	30/10/2009		

II/0020	To introduce an additional manufacturing site for H1N1 antigen finished product. Update of or change(s) to the pharmaceutical documentation	22/10/2009	26/10/2009		
II/0015	To introduce some changes for the storage of the antigen. Change(s) to container	24/09/2009	05/10/2009		
II/0008	To introduce some changes in the manufacturing process for the adjuvant emulsion at the bulk stage. Change(s) to the manufacturing process for the finished product	24/09/2009	05/10/2009		
IB/0016	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	30/09/2009	n/a		
PU/0017	To update the composition of the strain of Pandemrix to the officially recommended by WHO and CHMP for the Pandemic Influenza, which is A/California/07/2009 (H1N1)v like strain. Pandemic Update	24/09/2009	29/09/2009	SmPC, Annex II, Labelling and PL	
II/0013	Change(s) to shelf-life or storage conditions	24/09/2009	29/09/2009	SmPC	
IB/0014	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	11/09/2009	n/a		

II/0012	To introduce some changes in the manufacturing site for the production of the active substance. Update of or change(s) to the pharmaceutical documentation	20/08/2009	08/09/2009		
II/0011	To introduce the use of alternative shipping containers to the manufacturing process for the active substance. Change(s) to container	20/08/2009	08/09/2009		
II/0006	To update section 5.1 of the SPC regarding the interval between 2 doses for the primary schedule vaccination based on data from a clinical trial. The PL was updated to reflect the results of user testing. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	07/07/2009	SmPC and PL	In a clinical trial, two doses of A/Vietnam AS03 adjuvanted vaccine were needed to meet and exceed all three CHMP criteria for responses to homologous virus. The results were observed when the two doses were given either 21 days apart or 6 months apart. A single dose of A/Vietnam AS03 adjuvanted vaccine followed by a dose of A/Vietnam or A/Indonesia AS03 adjuvanted vaccine at Month 6 elicited haemagglutinin inhibition responses to homologous and heterologous booster strains that met and exceeded the CHMP criteria at Month 6 + 7 days post-boost with further increments at Month 6 + 21 days. Therefore based on immunogenicity and safety data, the product information was updated to reflect that two doses of AS03-adjuvanted vaccine given 6 months apart give comparable immune responses after the second dose to two doses given 21 days apart. The PL was updated further to a test performed to increase its readability.
II/0005	To update sections 4.2 and 5.1 of the SPC to include treatment in subjects aged 61 years and above based	29/05/2009	07/07/2009	SmPC and PL	Please refer to the Scientific Discussion: Pandemrix-H-C-832-II-05-AR

	on clinical trial data. Annex II and the PL were updated accordingly. The marketing authorisation holder took the opportunity to introduce minor corrections in the SPC and labeling and to correct the contact details for Cyprus, Denmark, Latvia and Slovakia in the PL. Extension of Indication				
II/0004	To update sections 4.2, 4.4 and 5.1 of the SPC to include the possibility of a booster dose after primary immunisation with two doses of the marketing authorisation holder's (MAH) prepandemic vaccine containing antigen from the same subtype, based on data from clinical trials. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	07/07/2009	SmPC and PL	Based on immunogenicity and safety data from clinical trials, the product information was updated to reflect that a single dose of Pandemrix might be given to subjects who have previously received one or two doses of the MAH's AS03 adjuvanted prepandemic influenza vaccines. It has to be noted that the data are specific to the administration of H5N1 vaccine of a clade following one or two doses of H5N1 of a different clade.
II/0010	To introduce a change in the manufacturing process of the H5N1 antigen active substance. Change(s) to the manufacturing process for the active substance	25/06/2009	01/07/2009		
II/0009	To introduce some changes to the manufacturing process of the antigen H5N1. Change(s) to the manufacturing process for the active substance	25/06/2009	01/07/2009		

II/0001	Introduction of an additional filling, labelling and packaging site for the adjuvanting system. Change(s) to the manufacturing process for the finished product	20/11/2008	15/12/2008		
IB/0003	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	29/09/2008	n/a		
IA/0002	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	30/07/2008	n/a	Annex II	