ProQuad

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
IA/0159/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or	21/07/2022		Annex II	

[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).

	manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IG/1506	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	31/05/2022	n/a		
PSUSA/1936/ 202109	Periodic Safety Update EU Single assessment - measles / mumps / rubella / varicella vaccines (live)	05/05/2022	n/a		PRAC Recommendation - maintenance
T/0156	Transfer of Marketing Authorisation	14/03/2022	13/04/2022	SmPC, Labelling and PL	
II/0154	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	20/01/2022	n/a		
WS/2142	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test	09/12/2021	n/a		

	method or a method using a biological reagent for a biological AS				
WS/2119/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation 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	18/11/2021	n/a		
II/0151/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/09/2021	13/04/2022	SmPC and PL	
IB/0150	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	18/08/2021	n/a		
N/0148	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2021	13/04/2022	Labelling and PL	

WS/2062	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	10/06/2021	n/a		
IA/0149/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	08/06/2021	n/a		
IB/0147	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	28/05/2021	n/a		
IG/1375	A.7 - Administrative change - Deletion of	25/03/2021	n/a		

	manufacturing sites				
II/0144	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	21/01/2021	n/a		
II/0143	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	10/12/2020	n/a		
IA/0142/G	This was an application for a group of variations. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	25/09/2020	09/07/2021	SmPC and Labelling	
WS/1889/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a	03/09/2020	n/a		

	specification parameter which may have a significant effect on the overall quality of the AS and/or the FP				
WS/1787/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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.	28/05/2020	n/a		
II/0139	To update sections 4.4 and 4.8 of the SmPC to update the safety information and further characterize the risk of secondary transmission following MAH evaluation of new significant Pharmacovigilance data. The Package Leaflet is updated accordingly. The RMP has been updated to version 7.1 to reflect those changes and with the consequential revisions: the important potential risk of "potential secondary transmission of Oka/Merck varicella vaccine virus	14/05/2020	09/07/2021	SmPC, Annex II, Labelling and PL	The review of Proquad post-marketing data has demonstrated that transmission of varicella vaccine virus (Oka/Merck strain) resulting in varicella infection including disseminated disease may rarely occur between vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella, including healthy as well as high risk individuals. For more information, please refer to the Summary of Product Characteristics.

	strain in susceptible high-risk individuals leading to severe clinical consequences" is renamed to "secondary transmission of Oka/Merck varicella vaccine virus strain in susceptible individuals leading to disseminated disease" and is reclassified to important identified risk. The MAH takes the opportunity to implement some changes in Section 6.5 of the SmPC with information on the glass type for the immediate container following the "Excipients in the labelling and package leaflet of medicinal products for human use guideline" and the "Guideline on quality aspects included in the product information for vaccines for human use". Annex A has been updated with the same information. In addition, the MAH implements QRD v10.1 taking into account the 'Compilation of QRD decisions on stylistic matters in product information' (EMA/25090/2002 rev.19. The MAH also takes the chance to align some wordings across other MMRV vaccines owned by the MAH, in particular section 6.6 'Special precautions for disposal and other handling'. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				

IG/1191/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	06/03/2020	n/a		
N/0137	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2020	09/07/2021	PL	
WS/1740	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	23/01/2020	n/a		

II/0134	Submission of an updated RMP (version 6.1) in order to adhere to Version 2 of the RMP template. As a consequence, the following changes are carried out: - Removal of the important identified risks febrile seizure, fever, measles-like rash, and thrombocytopenia and the addition of disseminated disease caused by Oka/Merck vaccine virus strain. - The important potential risks varicella-like or herpes zoster-like rashes, potential central nervous system events, potential transmission of varicella vaccine virus strain, exposure of immunocompromised individuals, hypersensitivity including anaphylaxis and injection-site reactions are also removed. - Additionally, secondary transmission of Oka/Merck vaccine virus strain in susceptible high-risk individuals leading to severe clinical consequences is included. - The important missing information 'categories exposure during pregnancy' and 'safety and immunogenicity in patients less than 9 months' of age is also removed. 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	03/10/2019	n/a		

IG/1119/G	This was an application for a group of variations. 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	20/06/2019	n/a		
WS/1583	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/05/2019	n/a		
PSUSA/1936/ 201809	Periodic Safety Update EU Single assessment - measles / mumps / rubella / varicella vaccines (live)	16/05/2019	n/a		PRAC Recommendation - maintenance
II/0132	B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	04/04/2019	n/a		
WS/1578	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.c - Change in the specification parameters and/or limits of an AS, starting	04/04/2019	n/a		

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
WS/1512	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.z - Change in container closure system of the Finished Product - Other variation	17/01/2019	n/a		
IG/0977	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	19/10/2018	n/a		
WS/1392	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC of ProQuad and Varivax in order to reflect that complications of varicella from vaccine strain including herpes zoster and disseminated diseases such as aseptic meningitis and encephalitis have been reported in immunocompromised or immunocompetent individuals. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the product information and to update the list of local representatives in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to	18/10/2018	21/10/2019	SmPC and PL	Complications of varicella from vaccine strain including herpes zoster and disseminated diseases such as aseptic meningitis and encephalitis have been reported in immunocompromised or immunocompetent individuals.

	new quality, preclinical, clinical or pharmacovigilance data				
IG/0973	A.7 - Administrative change - Deletion of manufacturing sites	21/09/2018	n/a		
IB/0126	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	19/07/2018	n/a		
IB/0124/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	27/03/2018	n/a		
N/0123	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2018	21/10/2019	Labelling	
WS/1325	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	18/01/2018	n/a		

	B.II.z - Quality change - Finished product - Other variation				
WS/1199/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.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.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	16/11/2017	n/a		
IG/0856/G	This was an application for a group of variations. 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.f.1.e - Stability of FP - Change to an approved stability protocol	10/11/2017	n/a		
IB/0119	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure	26/07/2017	n/a		

	(including replacement or addition)				
II/0114	Update of section 4.8 of the SmPC in order to change the frequency of the adverse reaction Henoch-Schönlein purpura from 'not known' to 'rare'. In addition, the MAH took the opportunity to make editorial changes in the product information and to make corrections in the Finnish and Swedish product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/05/2017	18/12/2017	SmPC	
N/0118	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/04/2017	18/12/2017	PL	
IG/0777	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2017	18/12/2017	SmPC, Labelling and PL	
WS/1029	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	19/01/2017	n/a		
IG/0758	A.1 - Administrative change - Change in the name and/or address of the MAH	11/01/2017	18/12/2017	SmPC, Labelling and	

				PL	
N/0115	Update of the package leaflet with revised contact details of the local representatives. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2016	18/12/2017	PL	
WS/0989	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/12/2016	n/a		
IG/0741	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/11/2016	n/a		
WS/0983	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	06/10/2016	n/a		
WS/0947	This was an application for a variation following a worksharing procedure according to Article 20 of	28/07/2016	n/a		

	Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol				
WS/0739	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	21/07/2016	n/a		
IG/0696	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	20/06/2016	n/a		
IG/0695	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/06/2016	n/a		
IG/0687	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	30/05/2016	n/a		

PSUSA/1936/ 201509	Periodic Safety Update EU Single assessment - measles / mumps / rubella / varicella vaccines (live)	14/04/2016	n/a		PRAC Recommendation - maintenance
IB/0104	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/03/2016	n/a		
R/0100	Renewal of the marketing authorisation.	22/10/2015	16/12/2015	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 this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of ProQuad continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
IG/0625	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	16/11/2015	n/a		
II/0101	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	12/11/2015	n/a		
WS/0786	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.z - Change in control of excipients in the Finished Product - Other variation	17/09/2015	n/a		

N/0098	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2015	16/12/2015	PL	
WS/0718	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	21/05/2015	n/a		
WS/0706	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	21/05/2015	n/a		
WS/0693/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	23/04/2015	n/a		

	of the AS				
PSUSA/1936/ 201409	Periodic Safety Update EU Single assessment - measles / mumps / rubella / varicella vaccines (live)	10/04/2015	n/a		PRAC Recommendation - maintenance
WS/0664/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/03/2015	n/a		
WS/0626	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	18/12/2014	n/a		
IG/0511	A.4 - Administrative change - Change in the name	08/12/2014	n/a		

	and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
WS/0644	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change to in-process tests or limits applied during the manufacture of the active substance B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	20/11/2014	n/a		
WS/0492	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the ProQuad and M-M-RVaxpro SmPC to clarify that in severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine, measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported; disseminated mumps and rubella vaccine virus infection has also been reported. Further, minor	20/11/2014	12/01/2015	SmPC, Annex II, Labelling and PL	A published article, which described a study of more than two million children, suggested that MMR vaccines were not associated with an increased risk of encephalopathy after vaccination per se. However, measles inclusion body encephalitis, pneumonitis and death as a direct consequence of disseminated measles vaccine virus infection have been reported post-marketing in severely immunocompromised individuals that were - in spite of the contraindication - vaccinated with measles-containing vaccines. As a consequence, the existing statement in the product information concerning encephalitis and encephalopathy was clarified.

	editorial changes have been implemented in the Package Leaflet and SmPC for ProQuad, the M-M-RVaxpro annexes have been aligned with the latest QRD template version 9.0 and minor editorial changes implemented in the labelling for M-M-RVaxpro. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0493	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	21/10/2014	n/a		
IG/0487	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	10/10/2014	n/a		
IB/0088	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	24/09/2014	n/a		
N/0086	Update of Annex IIIA in order to improve readability of the labelling Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/07/2014	12/01/2015	Labelling	

WS/0479	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. to add a site responsible for performing release testing of varicella drug substance B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	24/07/2014	n/a		
WS/0548/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	26/06/2014	n/a		
IG/0435	A.1 - Administrative change - Change in the name and/or address of the MAH	06/05/2014	12/01/2015	SmPC, Labelling and PL	

IG/0436	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	30/04/2014	n/a		
IB/0080	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)	25/04/2014	n/a		
II/0078/G	This was an application for a group of variations. Additional manufacturing facility for varicella active substance and addition of a new in-process test and limit applied during the manufacture of varicella drug substance B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	25/04/2014	12/01/2015	Annex II	
PSUSA/1936/ 201309	Periodic Safety Update EU Single assessment - measles / mumps / rubella / varicella vaccines (live)	10/04/2014	n/a		PRAC Recommendation - maintenance
IG/0434	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV	09/04/2014	n/a		

	(including contact details) and/or changes in the PSMF location				
IAIN/0079	B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR	17/03/2014	n/a		
II/0073/G	This was an application for a group of variations. major changes to the manufacturing process of the active substance. Change in test procedure for the finished product. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	23/01/2014	12/01/2015	SmPC and PL	
II/0075	Change in the manufacturer of a raw material for AS	18/12/2013	n/a		

	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				
WS/0438	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update section 4.8 of the SmPCs of Proquad and Varivax to include "necrotizing retinitis" based on a post marketing safety report in an immunocompromised individual. In addition, Section 4.3 of the SmPCs was updated to include references to section 4.8 and vice versa. The MAH took also the opportunity to update the Product Information for Varivax with the last version of the QRD template for MRP/DCP products (version 3). C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/11/2013	18/12/2013	SmPC	A post marketing report of necrotizing retinitis in an immunocompromised individual was identified during routine safety surveillance for varicella virus vaccine, live (Oka/Merck). Specimens from the patient's eye were positive for DNA from the Oka strain of varicella-zoster virus (VZV). Live varicella vaccines are contraindicated in immunocompromised individuals, and the addition of necrotizing retinitis to the Product Information is intended to inform healthcare professionals (HCPs) that this condition has been reported in immunocompromised individuals following vaccination. This addition is relevant for ProQuad since varicella virus vaccine, live (Oka/Merck) is one of the vaccine components in ProQuad. This addition also aims at informing HCPs that the eye may be the only involved organ at the time of presentation.
WS/0418/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. minor change to test procedure for active substance and finished product	24/10/2013	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
X/0068	Addition of a new route of administration, Intramuscular use. Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC were updated to reflect the new data. The Package Leaflet and Labelling were updated in accordance. The annex II was updated according to the latest QRD template. Annex I_2.(e) Change or addition of a new route of administration	30/05/2013	31/07/2013	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion of the Assessment Report Proquad-H-622-X-68-VAR-en.
WS/0404/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. Update of analytical methods in order to align with compendial procedures and guidances B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	25/07/2013	n/a		

	or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
WS/0363	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes in the manufacturing process of the active substance B.I.a.2.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	25/04/2013	n/a		
WS/0349	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. change in the test procedure of the active substance B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	25/04/2013	n/a		

A20/0060	Art 20 review: Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 March 2012, the opinion of the CHMP further to the evaluation of the recent published data and post marketing surveillance regarding the vaccination with measles, mumps, rubella and varicella vaccines in pregnant women and immunocompromised subjects. The CHMP was requested to assess the impact thereof on the risk-benefit balance of ProQuad in these specific populations and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn.	13/12/2012	18/02/2013	SmPC, Annex II and PL	Please refer to the Assessment Report: ProQuad-H-622-A20-60-Assessment Report-Article 20
IG/0261/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	30/01/2013	n/a		
WS/0302	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	13/12/2012	n/a		

	to introduce a second PSF skid for the manufacture of varicella vaccine bulk 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				
WS/0261	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in the specification of the varicella clarified bulk 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	20/09/2012	20/09/2012		
IB/0064	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	12/07/2012	n/a		
WS/0259	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in batch size of intermediate B.I.a.3.a - Change in batch size (including batch size	21/06/2012	21/06/2012		

	ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size				
II/0055	Extension of indication to include use from 9 months of age onwards under special circumstances. Furthermore, the PI is being brought in line with the latest QRD template. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/03/2012	20/04/2012	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion of the Assessment Report Proquad-H-622-II-55-AR.
II/0056	Update of sections 4.8 and 5.1 of the SmPC with Herpes Zoster incidence and 15-year effectiveness data based on post licensure studies on long-term effectiveness of a varicella vaccine (VARIVAX) as requested by CHMP following the assessment of Follow-up Measures FU2 -011.1, -012.1 and -013.4. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	16/02/2012	19/03/2012	SmPC	In support of this variation, the MAH provided data derived from two long-term follow-up studies with Varivax (monovalent varicella vaccine) evaluating long-term persistence of protective post vaccination antibodies to varicella with special regard to an epidemiologically changing environment and the rate of breakthrough cases. Study 036 was a 15-year observational prospective cohort study, which studied long-term antibody persistence of varicella vaccine among children and adolescents and evaluated the risk of herpes zoster (HZ) in vaccinated individuals in a 15-year long-term follow-up. Study 037 was a cross-sectional epidemiological survey to evaluate the changing epidemiology of varicella among children and adolescents. Both studies showed no increase in the frequency of herpes zoster compared to children with prior wild type varicella during the pre vaccine era and that varicella vaccinated children actually may have a lower risk of herpes zoster.

					The data confirmed that widespread varicella vaccination reduces the risk of varicella by approximately 90% and that protection is maintained over at least 15 years both in vaccinated and unvaccinated individuals. The Product information was updated with more detailed results from these studies.
WS/0225	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in batch size (including batch size ranges) of active substance or intermediate B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	15/03/2012	15/03/2012		
IG/0159	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	09/03/2012	n/a		
IG/0156	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	24/02/2012	n/a		
II/0054	To update section 4.8 to include "varicella (vaccine strain)" as an adverse event under the SOC Infection and infestations". The PL is updated accordingly.	19/01/2012	21/02/2012	SmPC and PL	The revision of the product information was based on reports of cases of varicella from immunocompetent patients following the administration of VARIVAX, which contains the same varicella virus component as Proquad.

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				The presence of Oka/Merck or vaccine-strain varicella zoster virus was identified in rash specimens of these cases. Similar reports for ProQuad have not been received.
II/0053	To update section 4.5 of the SmPC and section 2 of the Package Leaflet to include information on coadministration with the hexavalent vaccine Infanrix Hexa. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	21/02/2012	SmPC and PL	Study X06-MMRV-302 was designed to assess the immunogenicity and safety of concomitant administration of ProQuad with Infanrix hexa, when a first dose of ProQuad is administered to subjects from 12 to 23 months of age concomitantly with a booster dose of Infanrix hexa either as a third dose (2+1 schedule) or a fourth dose (3+1 schedule). The immunogenicity results demonstrate that following concomitant administration of ProQuad with Infanrix hexa no clinically relevant interference in the antibody response to each of the individual antigens is observed. Generally higher response rates and antibody titres were obtained, when both vaccines were given concomitantly compared to the administration of each vaccine alone. The immunisation schedule (3+1 vs 2+1) had limited impact on the immunogenicity results. As to be expected after concomitant administration a higher percentage of adverse reactions were observed than after administration of each vaccine alone. More subjects reported at least one solicited injection-site adverse reaction related to ProQuad in the concomitant group compared to the non-concomitant group, whereas a numerically comparable number of subjects reported systemic adverse events related to ProQuad in both groups. The frequency of adverse reactions in the concomitant group is comparable with that of the combined frequency of adverse reactions found after administration of both vaccines alone. Only non-injection site varicella-like rashes

					were reported more frequently in the concomitant group compared to the ProQuad alone. The safety profile following concomitant administration is comparable in terms of incidence and nature of adverse events to that following separate administration of the vaccines. All observed adverse events are already known and described in the SmPCs. However higher rates of high fever were observed in recipients of ProQuad given concomitantly with Infanrix hexa compared to Infanrix hexa alone. The Product information was therefore updated with this findings and to reflect that ProQuad can be given concomitantly with either Prevenar and/or Hepatitis A vaccine, or with monovalent or combination vaccines comprised of diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, inactivated poliomyelitis, or hepatitis B antigen.
II/0043	Change in test procedure for the active substance. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	17/11/2011	17/11/2011		
II/0041	To update section 4.8 of the SmPC to reflect the information on injection site adverse reactions after the second dose following the CHMP's assessment of the clinical study MRV01C (FUM041). In addition the MAH took the opportunity to include the date of last renewal in the SmPC, to align the section on Braille in the labelling with the QRD template and to amend	21/07/2011	05/09/2011	SmPC, Labelling and PL	In 8 clinical studies carried out either with M-M-Rvaxpro or an M-M-R-Varicella vaccine the frequency of the overall adverse reactions and fever cases post dose 2 was lower or similar to post dose 1. Higher rates of injection site reactions were however found after dose 2 compared to dose 1 in most of the clinical trials with significantly higher rates in three studies. Comparable rates of injection site

	the list of local representatives in the PI. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				reactions were reported from trials where ProQuad was administered concomitantly with other vaccines or from trials conducted during vaccine development. These findings were reflected in the SmPC. In conclusion the proposed wording of the SmPC section 4.8 should be slightly modified as follows: 'however, the rates of injection-site erythema and swelling were similar to or in general higher after the second dose than after the first dose'.
IG/0093	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	12/08/2011	n/a		
IG/0085	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	08/07/2011	n/a		
IB/0040	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	29/04/2011	n/a		
IG/0059/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	15/04/2011	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
R/0034	Renewal of the marketing authorisation.	20/01/2011	17/03/2011	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 ProQuad remains positive, but considers that its safety profile is to be closely monitored for the following reasons: Very limited post authorisation safety data are available regarding the use of ProQuad (refrigerated formulation) within the EU. Furthermore, most of the clinical trials were conducted with the frozen vaccine formulation in the US. Additionally, a potential increased risk of febrile seizures observed in the 5- to 12-day timeframe after the first dose of quadrivalent measles, mumps, rubella and varicella vaccines in children compared to concomitant administration of measles, mumps, rubella and varicella vaccines might be a signal that also other side effects might occur more frequently after administering ProQuad compared to concomitant administration of measles, mumps, rubella and varicella vaccines. The CHMP decided that the MAH should continue to submit 6-monthly PSURs. Therefore, based upon the safety profile of ProQuad, which requires the submission of 6-monthly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0037/G	This was an application for a group of variations. Update of SmPC, Annex II and Package Leaflet Update of sections 4.4 and 4.8 of the SmPC based	20/01/2011	28/02/2011	SmPC, Annex II and PL	This procedure is a grouping of two type II variations. One was submitted to update sections 4.4 and 4.8 of the SmPC and section 4 of the PIL to include information on secondary transmission to a healthy non-vaccinee of the

	upon a safety report about a secondary transmission of Oka vaccine strain VZV from a vaccinee who did not develop a rash post vaccination with varicella virus vaccine live (Oka/Merck) to a healthy non-vaccinee. The PL was updated accordingly. The MAH took this opportunity to delete from Annex IIB the version of the DDPS, following CHMP request, and to update the list of local representatives. Moreover sections 4.4, 4.8 and 5.1 of the SmPC were updated to include additional information on febrile seizures and general safety based on the final report for the Large-Scale Observational Post-Licensure Study of the Short-Term Safety of ProQuad. The PL was 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Oka vaccine strain of VZV from a vaccinee who did not develop a rash post vaccination with a live attenuated varicella virus vaccine (strain Oka/Merck). The MAH took this opportunity to delete from Annex IIB the version of the DDPS as per October CHMP request. For the second type II, based on the final report for the Large-Scale Observational Post-Licensure Study of the Short-Term Safety of ProQuad, additional information was included in sections 4.4, 4.8 and 5.1 on the increased risk of febrile seizures only in the 5- to 12-day timeframe whilst no safety concerns were indentified in the 30-day period after the first or second dose, in comparison with the concomitant administration of the MMR and Varicella vaccines.
WS/0099/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 change the manufacturer of a reagent. To update certificates of suitability.	17/02/2011	17/02/2011		

	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
IB/0039/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	15/02/2011	n/a		
IB/0038	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	17/12/2010	n/a		
II/0036	Change to an in-process test applied during the manufacture of the finished product. B.II.b.5.d - Change to in-process tests or limits	18/11/2010	25/11/2010		

	applied during the manufacture of the finished product - Deletion of an in-process test which may have a significant effect on the overall quality of the finished product				
WS/0044	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To implement a change in the immediate packaging of the finished product. 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	23/09/2010	25/10/2010	SmPC and PL	
IB/0035	Change on the test procedure of a reagent. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	07/10/2010	n/a		
WS/0019/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c. Changes in the manufacturing process of	23/09/2010	23/09/2010		

	the active substance. The change refers to a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol. B.I.a.4.b. Change to in-process tests or limits applied during the manufacture of the active substance. Addition of a new on-process test and limits. 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 B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits				
WS/0017/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2 Changes in the manufacturing process of the active substance c) The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol. B.I.b.1 Change in the specification parameters	23/09/2010	23/09/2010		

	and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance a) Tightening of specification limits for medicinal products subject to Official Batch Release 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 B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to Official Batch Release				
II/0031	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	22/07/2010	06/09/2010	SmPC, Annex II and PL	Following the Assessment to PSUR No. 8, the CHMP requested the MAH to submit a variation to update the EUSPC regarding ProQuad and thrombocytopenia due to a cluster of cases observed in Italy. During the assessment, it became apparent that although many of the cases reported worldwide (in total 20 cases) had confounding factors that could explain the onset of thrombocytopenia, the data indicated that individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination with Proquad. The CHMP therefore agreed to update the Product Information to reflect this data. In addition, a warning has been included that individuals who experienced thrombocytopenia following the first dose of a live measles, mumps, and rubella vaccine may develop thrombocytopenia with repeat doses.

WS/0018	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 the test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance. Other changes to a test procedure (including replacement or addition) of the active substance or a starting material/intermediate. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	22/07/2010	22/07/2010		
IA/0030	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	30/04/2010	n/a		
IA/0029/G	This was an application for a group of variations. To change in the name of the Drug substance and drug product manufacturer. Following the merger between Merck & Co., Inc. and Schering-Plough Corporation, the name of the company has changed from Merck & Co., Inc. to Merck Sharp & Dohme Corp.	26/03/2010	n/a	Annex II	

	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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)				
II/0028	Change(s) to the manufacturing process for the finished product	18/03/2010	24/03/2010		
II/0027	To scale-up the number of production roller bottles planted during the manufacture of Varicella Harvested Virus Fluid process. Update of or change(s) to the pharmaceutical documentation	18/02/2010	01/03/2010		
II/0026	Update of the detailed description of pharmacovigilance system (DDPS) including the change of the Qualified Person Responsible for Pharmacovigilance (QPPV). The version number of the DDPS in Annex II has been updated accordingly. Update of DDPS (Pharmacovigilance)	17/12/2009	19/01/2010	Annex II	The DDPS has been updated to version 2.0 in order to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements
II/0025	Change(s) to the test method(s) and/or specifications for the active substance	17/12/2009	06/01/2010		

II/0024	Change(s) to shelf-life or storage conditions	22/10/2009	30/10/2009		
IA/0023	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/07/2009	n/a		
II/0018	To update sections 4.5, 4.8 and 5.1 of the SPC to include information on the concomitant use of ProQuad with pneumococcal conjugate vaccine and/or hepatitis A vaccine. These changes are based on a clinical study on the immunogenicity and safety of Proquad when given concomitantly with a pneumococcal conjugate vaccine, a study on the safety of the concomitant administration of Proquad and a hepatitis A vaccine and a study evaluating the immunogenicity and safety of concomitant administration of Proquad, hepatitis A vaccine and pneumococcal conjugate vaccine. The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	01/07/2009	SmPC and PL	The modification sought in this application was to obtain approval for the concomitant administration of ProQuad with pneumococcal conjugate vaccine and/or hepatitis A vaccine. The coadministration of ProQuad with the pneumococcal conjugate vaccine Prevenar showed no impact on the antibody responses of both vaccines. Regarding concomitant use of ProQuad and VAQTA data on the concomitant use of the vaccines MMR II and Varivax (the same antigens are contained in ProQuad) with and without VAQTA showed that immune responses to measles, mumps and rubella 6 weeks after administration to infants at 12 months of age were similar. In a further study, concomitant use of ProQuad, Prevenar and VAQTA revealed also no clinically relevant interference of the antibody response against each of the individual antigens. In terms of safety, ProQuad demonstrated to have an acceptable safety profile in children from 12 to 15 months of age, when administered together with Prevenar, when VAQTA or when all three vaccines were given concomitantly. However, an increased rate of vaccine-related pyrexia could be observed in general when ProQuad was coadministered with other vaccines than given alone. The use of anti-inflammatory drugs was therefore more

					frequent in the group with concomitant vaccine administration. Overall, the available data showed a sufficient level of efficacy and safety for the coadministration of ProQuad when given in combination with Prevenar and/or VAQTA.
IA/0022	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	09/06/2009	n/a		
IB/0021	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	29/05/2009	n/a		
II/0017	Update of the section 4.8 of the Summary of Products Characteristics to include further information on febrile seizures following a CHMP request. Additionally the MAH took the opportunity to update the list of local representatives in Malta, Latvia and Denmark in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC and PL	Following a CHMP request, the MAH modified the section 4.8 of the Summary of Products Characteristics (SPC) to add new information on febrile seizures in children with the information on a clinical study on the short-term safety of ProQuad after the administration of one dose. Based on the review of clinical data, the safety study conducted by Merck revealed an increased risk of febrile convulsion in children vaccinated with ProQuad compared to children receiving MMR and varicella vaccine concomitantly. In summary these data suggest that the risk of febrile convulsion after vaccination with ProQuad may be increased ~2 fold in days 5-12 (when post-vaccination fever is most likely to occur), compared to concomitant vaccination, but is not different overall in the month following vaccination in children vaccinated with ProQuad compared to a historical comparison group.
IA/0020	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	25/03/2009	n/a		

II/0014	Change(s) to the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	23/10/2008	03/11/2008		
II/0013	Change(s) to the manufacturing process of the active substance Change(s) to the test method(s) and/or specifications for the active substance	23/10/2008	03/11/2008		
II/0016	Changes to the manufacturing process of the drug product. Change(s) to the manufacturing process for the finished product	25/09/2008	01/10/2008		
II/0015	Addition of an alternate site (to perform manufacturing and release testing) . Change(s) to the test method(s) and/or specifications for the finished product	24/07/2008	01/08/2008		
II/0012	Update of Summary of Product Characteristics and Package Leaflet To add epididymitis in section 4.8 of the SPC. In addition the list of all adverse events in section 4.8 was updated to one single list including adverse events from clinical studies and post marketing	24/04/2008	20/06/2008	SmPC and PL	As a result of a review of adverse experiences reported for a vaccine comparable to ProQuad from the same manufacturer but without the varicella component, the Product Information was updated to include as an adverse event epididymitis in the EU Product Information. Epididymitis is a common complication of infection by wild

	surveillance and the SPC was updated in compliance with the latest QRD template. The list of local representatives was updated to add Bulgaria and Romania and amend other contact details. Update of Summary of Product Characteristics and Package Leaflet				mumps virus and it was considered biologically possible that a small number of patients may develop similar complications after vaccination. In reviewing the spontaneous reports, from market introduction up until 10 September 2007, 13 cases of epididymitis were identified that could be temporally associated with the administration of the measles, mumps and rubella vaccine.
IA/0011	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	22/01/2008	n/a		
IB/0009	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	11/10/2007	n/a		
II/0007	Quality changes	20/09/2007	25/09/2007		
IA/0006	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	22/05/2007	n/a		
II/0005	Change(s) to the test method(s) and/or specifications for the active substance	22/03/2007	26/03/2007		
IB/0004	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	30/01/2007	n/a		
II/0001	Quality changes To develop a refrigerator-stable formulation of the finished product to change the storage conditions from -15ºC to 2ºC-8ºC. Change(s) to the test method(s) and/or	27/07/2006	12/09/2006	SmPC, Labelling and PL	The Marketing Authorisation Holder (MAH) has developed a refrigerator-stable formulation of the finished product to change the storage conditions from -15ºC to 2ºC-8ºC . This manufacturing change was supported by Quality and Clinical documentation. Furthermore the MAH also proposed to set further specifications in the manufacturing

	specifications for the active substance Change(s) to shelf-life or storage conditions				of the varicella Drug Substance. The product information has been updated accordingly.
IA/0002	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	09/06/2006	09/06/2006	SmPC, Labelling and PL	
IA/0003	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	07/06/2006	n/a		