Rotarix

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IB/0134	C.I.7.a - Deletion of - a pharmaceutical form	20/05/2024		SmPC, Labelling and PL	
II/0133/G	This was an application for a group of variations.	02/05/2024	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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.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				
II/0132/G	This was an application for a group of variations. 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 originally approved batch size 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	14/03/2024	n/a		
IB/0131	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	22/01/2024	n/a		
IB/0130	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/07/2023		SmPC, Labelling and PL	

IB/0129/G	This was an application for a group of variations. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.c.2.z - Change in test procedure for an excipient - Other variation	26/07/2023	n/a		
PSUSA/2665/ 202207	Periodic Safety Update EU Single assessment - rotavirus vaccine monovalent (live, oral)	16/03/2023	n/a		PRAC Recommendation - maintenance
II/0128	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	12/01/2023	n/a		
WS/2325	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	17/11/2022	n/a		
II/0125	Submission of the final report from study EPI-ROTA-052 BOD EU SUPP (201433) listed as a category 3	10/06/2022	n/a		

	study in the RMP. This is an Observational community-based strain surveillance study to monitor the potential emergence and spread of novel RV strains throughout Europe. RMP version 23 has been approved with this procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0124	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	07/02/2022	n/a		
IB/0123	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/01/2022	13/01/2023	SmPC, Labelling and PL	
N/0122	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2021	13/01/2023	PL	
IB/0121	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/08/2021	n/a		
IB/0120	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	15/02/2021	n/a		
WS/1987	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	11/02/2021	n/a		

	B.II.e.z - Change in container closure system of the Finished Product - Other variation				
WS/1912	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/11/2020	n/a		
IA/0118	A.7 - Administrative change - Deletion of manufacturing sites	02/10/2020	n/a		
II/0116/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	13/02/2020	01/02/2021	SmPC, Annex II, Labelling and PL	

PSUSA/2665/201907	Periodic Safety Update EU Single assessment - rotavirus vaccine monovalent (live, oral)	13/02/2020	n/a		PRAC Recommendation - maintenance
WS/1670	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.z - Quality change - Finished product - Other variation	25/07/2019	n/a		
IG/1096	A.7 - Administrative change - Deletion of manufacturing sites	29/05/2019	n/a		
IB/0112	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/04/2019	n/a		
PSUSA/2665/201807	Periodic Safety Update EU Single assessment - rotavirus vaccine monovalent (live, oral)	31/01/2019	25/03/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2665/201807.
WS/1529	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	21/03/2019	n/a		
IA/0110	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	24/10/2018	n/a		

II/0106/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.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 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	26/07/2018	25/03/2019	SmPC, Labelling and PL	The SmPC section 1, 6.3, 6.5, 6.6 and 8, Annex II has been updated to reflect the new Multi-monodose (5 single dose) squeezable tube presentation for Rotarix vaccine. The Labelling and PL have been updated accordingly. In addition, the list of local representatives in the PL is being revised.
IB/0107	B.II.b.3.f - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process of an aqueous oral suspension	02/07/2018	n/a		

IA/0108	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	13/06/2018	n/a		
IG/0921	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	08/05/2018	n/a		
N/0104	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/04/2018	25/03/2019	Labelling	
PSUSA/2665/ 201707	Periodic Safety Update EU Single assessment - rotavirus vaccine monovalent (live, oral)	08/02/2018	n/a		PRAC Recommendation - maintenance
WS/1269	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.c.1.z - Change in immediate packaging of the AS - Other variation	18/01/2018	n/a		
II/0100	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/09/2017	n/a		
IB/0101	B.II.z - Quality change - Finished product - Other variation	21/09/2017	n/a		

IB/0099	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.	28/07/2017	n/a		
WS/1154	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	09/06/2017	n/a		
IB/0098	B.II.d.2.z - Change in test procedure for the finished product - Other variation	06/06/2017	n/a		
II/0094	Submission of the final study report for EPI-ROTA-007 VS US DB (A phase IV, open, observational study of the safety of Rotarix, administered to a birth cohort in US States health insurance plans) which is listed in the section III.4.3 of the Risk Management Plan (RMP) version 16. Consequently a revised RMP (version 18) is submitted in order to update information in relation to: the EPI-ROTA-007 VS US DB study; the EPI-ROTA-052 BOD EU SUPP as agreed during variation EMEA/H/C/0639/II/0086. In addition, the MAH took this opportunity to further update the RMP with the new due date for submission of the final study report for ROTA-085	05/05/2017	n/a		

	PMS. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/2665/ 201607	Periodic Safety Update EU Single assessment - rotavirus vaccine monovalent (live, oral)	23/02/2017	20/04/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2665/201607.
II/0089	Update of section 5.1 to introduce effectiveness data following completion of ecological observational study EPI-ROTA-025 VE AU DB (114910) - An ecological study to assess impact of rotavirus vaccination on hospitalisations for rotavirus gastroenteritis (RV GE) in children <5 years of age in Australia. In addition, the marketing authorisation holder took the opportunity to introduce clarifications in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/03/2017	30/01/2018	SmPC	
IB/0095/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for	09/02/2017	n/a		

	sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.f - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process of an aqueous oral suspension B.II.b.3.f - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process of an aqueous oral suspension B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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 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 B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold				

	compared to the originally approved batch size B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IB/0096/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.c.2.z - Change in test procedure for an excipient - Other variation	02/02/2017	n/a		
IB/0093	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	15/12/2016	n/a		
II/0086	Submission of the final report of study EPI-ROTA-052 BOD EU SUPP (201433) in which the strain surveillance data of the European Rotavirus Network (EuroRotaNet) during the rotavirus seasons from September 2006 to August 2015 is presented. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/12/2016	n/a		The EuroRotaNet study does not provide evidence that rotavirus vaccination programmes are driving the emergence of vaccine escape strains that reverted to virulence. This conclusion should be taken with precaution because of the different limitations of the network, which is a good tool for overall surveillance of the main rotavirus types circulating throughout Europe, but which is not a suitable tool for detection of breakthrough disease or rare strains. The results of this study do not modify the benefit-risk balance of Rotarix, which remains positive.
IA/0092/G	This was an application for a group of variations.	27/10/2016	n/a		

	B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure				
IB/0090/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	28/09/2016	n/a		
IB/0088	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	22/08/2016	n/a		

IB/0087	B.II.e.z - Change in container closure system of the Finished Product - Other variation	08/08/2016	n/a		
IG/0679	B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	01/06/2016	n/a		
IB/0085	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/05/2016	n/a		
II/0083	Submission of results of study Rota-080, a blinded retrospective laboratory evaluation on archived serum samples from different clinical trials, to assess the serologic response to Porcine Circovirus type 1 (PCV-1) in infants aged 6 to 12 weeks following the oral administration of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus vaccine. These data are submitted as a follow-up of the PCV-1-related investigations from 2010 that were assessed by CHMP as part of the Article 20 procedure (EMEA/H/C/639/A-20/0024). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/02/2016	n/a		
PSUSA/2665/ 201507	Periodic Safety Update EU Single assessment - rotavirus vaccine monovalent (live, oral)	11/02/2016	n/a		PRAC Recommendation - maintenance

R/0079	Renewal of the marketing authorisation.	19/11/2015	14/01/2016	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 Rotarix continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
II/0078	B.II.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The change in shape or dimensions concerns a fundamental part, which may have a significant impact on the delivery, use, safety or stability of the FP	19/11/2015	14/01/2016	SmPC, Annex II and PL	
II/0081/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.3.f - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process of an aqueous oral suspension B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.f - Change in the batch size (including batch	15/10/2015	n/a		

	size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				
II/0062	Submission of the final report of genetic stability study EPI-ROTA-014 VS BE – 112560 to addresses the Post-Approval Measure ME2 005.2 in which the MAH commits to monitor for potential occurrence of genetic drifts and shifts in the vaccine strain in post-marketing settings; consequently, the RMP has been updated. Furthermore, the SmPC section 4.9 has been updated with information on cases of overdose. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	14/01/2016	SmPC	
IG/0540	A.7 - Administrative change - Deletion of manufacturing sites	26/06/2015	n/a		
II/0075	Submission of final CSR for study EPI-ROTA-020 BOD BE DB (114061) (A post-licensure, observational, ecological, database study to investigate the epidemiology of hospitalisations where rotavirus gastroenteritis (RV GE) is confirmed in children ≤ 5 years of age with opportunity to have been vaccinated with Rotarix™, and to investigate any impact in the change from lyophilised to liquid formulation of Rotarix™, in Belgium.) in fulfilment of MEA 045.1. The MAH took also the opportunity to	18/06/2015	n/a		

	submit responses to questions raised during assessment of the baseline report (CHMP opinion of 18 March 2010 for MEA 045) in fulfilment of MEA 045.2. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0077	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)	22/05/2015	n/a		
PSUSA/2665/ 201407	Periodic Safety Update EU Single assessment - rotavirus vaccine monovalent (live, oral)	12/02/2015	n/a		PRAC Recommendation - maintenance
WS/0591	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of final study report of a post-approval clinical study to compare the current and the new plunger stoppers and tip caps in response to a CHMP recommendation. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/11/2014	n/a		
II/0070/G	This was an application for a group of variations.	25/09/2014	n/a		

	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.3.f - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process of an aqueous oral suspension				
IB/0072	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/08/2014	n/a		
IG/0468	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	20/08/2014	n/a		
IG/0446	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	24/06/2014	n/a		
IB/0068	B.II.b.3.f - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process of an aqueous oral	06/06/2014	n/a		

	suspension				
WS/0511	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/05/2014	n/a		
II/0065	Reclassification of fill volume controls. B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	25/04/2014	n/a		
WS/0494	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/04/2014	n/a		
WS/0496	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or	25/04/2014	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0066	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/04/2014	08/04/2015	SmPC and PL	The CHMP requested the MAH in December 2013 to update the SmPC with a harmonised wording for rotavirus vaccines based on new epidemiological data that became available on intussusception. These data strengthen the existing evidence base that suggests a small increased risk of intussusception shortly after vaccination with Rotarix and Rotateq. A statement regarding any difference in risk between the two vaccines cannot, however, be made. Given that the vaccine attributable risk of intussusception remains small, the CHMP recommended that the balance of benefits and risks rotavirus vaccines remains favourable and requested the MAH that the SmPC should be updated to reflect that • Rotavirus vaccines carry an increased risk of intussusception, mostly within 7 days of vaccination. Up to 6 additional cases per 100,000 infants have been observed in the US and Australia against a background incidence of 33 to 101 per 100,000 infants (less than one year of age) per year, respectively. There is limited evidence of a smaller increased risk following the second dose. It remains unclear whether rotavirus vaccines affect the overall incidence of intussusception based on longer periods of follow up. • As a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools,

					abdominal bloating and/or high fever) since data from observational safety studies indicate an increased risk of intussusception, mostly within 7 days after rotavirus vaccination. Parents/guardians should be advised to promptly report such symptoms to their healthcare provider. The CHMP agreed that the wording proposed by the MAH submitted for this variation was in line with the CHMP request.
PSUV/0061	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance
WS/0439/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in the specification parameters of a raw material . B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of	18/12/2013	n/a		

	an obsolete parameter)				
IB/0059	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	29/11/2013	n/a		
WS/0443	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	24/10/2013	n/a		
WS/0381	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	24/10/2013	n/a		
IB/0058	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	11/10/2013	n/a		
IAIN/0057	B.II.d.1.b - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits for medicinal products subject to OCABR	04/09/2013	n/a		

II/0053	Changes in the the specification limits of a raw material. B.II.c.1.d - Change in the specification parameters and/or limits of an excipient - Change outside the approved specifications limits range	25/07/2013	n/a		
II/0047	To update section 5.1 'Pharmacodynamic properties' of the SmPC to include recently published real-world effectiveness and impact study data on the administration of Rotarix in different regions of the world, including Europe, Australia, Southeast Asia and Latin America in terms of protection against severe rotavirus gastroenteritis, hospitalisation rate and mortality. 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.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	20/11/2013	SmPC, Annex II and PL	This variation introduced results from vaccine effectiveness and impact studies in relation to vaccination with Rotarix from EU and non-EU countries. The data confirm that Rotarix protects in a real-life setting against severe rotavirus gastroenteritis (RV GE), including RV GE caused by G2P[4], but also highlight the potential for Rotarix to significantly reduce morbidity due to RV GE in children living in high and middle-income countries. Data on impact of Rotarix on public health impact of RV and all-cause GE-related mortality has also been reflected in the SmPC within this procedure.
II/0050	Additional manufacturer site for the finished product. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for	27/06/2013	n/a		

	biological/immunological medicinal products.				
IB/0054	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	20/06/2013	n/a		
IG/0306	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2013	n/a		
IG/0297	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2013	n/a		
IA/0049	B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	06/03/2013	n/a		
IG/0265/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	28/01/2013	n/a		
WS/0340	This was an application for a variation following a worksharing procedure according to Article 20 of	17/01/2013	n/a		

	Commission Regulation (EC) No 1234/2008. Change of specifications of reagent. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/11/2012	20/11/2013	SmPC, Annex II, Labelling and PL	To align the PI to the latest QRD template (version 8.0) and to update the list of local representative details for Belgium, Czech Republic and Luxemburg. This update applies to all formulations and presentations of Rotarix. In addition the MAH also takes the opportunity of this procedure to include the final version of the tube instructions for administration in Rotarix PI for the liquid formulation tube presentation following user testing as requested by the CHMP.
IB/0044	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)	24/08/2012	n/a		
IB/0043	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	18/06/2012	n/a		
WS/0201/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	19/01/2012	n/a		

	To propose new target fill volume controls. To align the volume specifications to be applied at release and during stability evaluation. To revise QC release procedures for final container volume determination. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IG/0133	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	22/11/2011	n/a		
IB/0035	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	25/10/2011	n/a		
II/0032	To update sections 4.4 and 5.1 of the SmPC to include efficacy data from trial Study Rota-028/029/030 in Asia that was extended up to the	22/09/2011	24/10/2011	SmPC and PL	Please refer to the scientific discussion of the Assessment Report: Rotarix-H-639-II-0032-VAR.

	age of 3 years. The MAH also took the opportunity to include minor editorial amendments in sections 4.2, 4.3 and 4.4 of the SmPC and to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IA/0034	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	29/09/2011	n/a		
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		
IA/0033	A.7 - Administrative change - Deletion of manufacturing sites	15/06/2011	n/a		
IB/0031	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	09/06/2011	n/a		
II/0029/G	This was an application for a group of variations. To update Section 4.4 to include rotavirus (RV) strains for which efficacy against RV gastroenteritis has been demonstrated based on efficacy results from Rota-037 and to update section 5.1 with data from this study.	14/04/2011	18/05/2011	SmPC	Additional efficacy data indicate that Rotarix protects against RV GE due to G8P[4] and G12P[6] confirm the ability of a monotypic RV strain G1P[8] to provide cross-protection against commonly and less commonly circulating RV strains. Although study Rota-037 was conducted in Africa, the

	To update the SmPC following the Vaccine Working Party (VWP) recommendation on rotavirus taxonomy adopted by CHMP in April 2009. 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.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				CHMP agreed that an update of the Rotarix European SmPC is relevant, taking into account that a pan-European surveillance study has identified RV strains of G8 and G12 type as emerging strains in Europe. The modifications and updates that proposed by the MAH were considered appropriate.
IG/0062/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	27/04/2011	n/a		
II/0030	Update of section 6.6 of the SmPC to prevent the risk of incorrect use of the Rotarix tube presentation. Annex IIB, Labelling and PL were revised accordingly. The MAH took also the opportunity to	17/02/2011	20/04/2011	SmPC, Annex II, Labelling and PL	Following reports of administration errors, the Product Information was updated to highlight the correct handling when opening the tube presentation. In addition, the MAH proposed additional measures to minimise the risk of

	delete duplications of handling instructions in section 6.6 and the PL of the other presentations. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				incorrect administration as follows: Health care professionals who are expected to use the Rotarix tube presentation are trained on the safe use of the product and provided with a health care professional training pack containing the following: - The updated Summary of Product Characteristics, - Training materials: recommendation pads with instruction for use, empty tubes (dummies), video/electronic materials for demonstration. The Educational materials should contain the following key message: - The tube presentation of Rotarix has a risk of medication errors therefore the health care professionals should follow strictly the instructions for opening to avoid the incorrect manipulation of the tube device and incorrect administration of the vaccine.
II/0026	To update the PI to reflect the most recent safety data from the Mexico PASS interim analysis. The update particularly concerns Section 4.4 and Section 4.8 of the SmPC. An update of the PL is also proposed to reflect these changes. 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	14/04/2011	SmPC and PL	Based on a surveillance study carried out by the MAH in Mexico, as well as additional post-marketing data including observed/expected calculations of spontaneously reported cases of intussusception and other surveillance data, which pointed towards a small increased risk of intussusception during the first week after the first dose of Rotarix, the Product information was updated as follows: No increased risk of intussusception was observed in clinical trials following administration of Rotarix when compared with placebo. Although no causal relationship has been established between vaccination with Rotarix and intussusception (see section 4.8). However, a small increased risk of intussusception in the 31-day period

					mostly within 7 days following the administration of the first dose of Rotarix cannot be excluded based on data from post-marketing safety studies. Therefore, as a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever). Parents/guardians should be advised to promptly report such symptoms.
IG/0052/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.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.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	18/03/2011	n/a		
R/0028	Renewal of the marketing authorisation.	18/11/2010	24/01/2011	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 Rotarix remains positive, but considers that its safety profile is to be closely monitored for the following reasons: Final data from post-authorisation safety studies are still

					awaited. Given the remaining questions regarding the risk of intussusception (IS) following administration of Rotarix, the regulatory authorities should be kept updated of the results of the ongoing post-authorisation safety studies to further study IS, as well as analyses of spontaneously reported IS cases. The CHMP considers that more safety experience needs to be gained about IS and recommended that the MAH should continue to submit yearly PSURs. Therefore, based on the safety profile of Rotarix, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0025	Update of SPC Sections 4.3 specifying that subjects with Severe Combined Immunodeficiency (SCID) disorder should not be vaccinated with Rotarix, and update of Section 4.8 to include gastroenteritis with vaccine viral shedding reported in infants with SCID based on data reported in PSUR 8. The PL is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	03/11/2010	SmPC, Annex II and PL	The product information is updated to reflect an observation of Gastroenteritis and vaccine virus shedding in infants with Severe Combined Immunodeficiency (SCID) disorder who had received Rotarix. Since live attenuated viral vaccines administered to SCID children could trigger an opportunistic infection, vaccination with Rotarix has been contraindicated in children with SCID.
A20/0024	Pursuant to Article 20 of Regulation (EC) No 726/2004 of 31 March 2004, the European Commission requested, on 23 March 2010, the opinion of the CHMP on the unexpected presence of a non-pathogenic viral strain of porcine circovirus 1 (PCV-1) DNA in Rotarix. The CHMP was asked to	22/07/2010	30/09/2010	Annex II	Please refer to the Assessment Report: Rotarix-H-639-A20-24-Assessment Report-Article 20.

	assess the impact of the findings on the quality of Rotarix, and to give its opinion on measures necessary to ensure the quality of this product, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.				
II/0027	Changes in the specifications of raw materials. B.II.c.1.d - Change in the specification parameters and/or limits of an excipient - Change outside the approved specifications limits range	23/09/2010	29/09/2010		
II/0020	Update of sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the Summary of Product Characteristics (SPC) to include reactogenicity and safety data from a pooled analysis of clinical trials conducted with either the lyophilised or the liquid formulation of Rotarix and post marketing data from both formulations. In addition to these changes, the MAH took the opportunity to add a reference to the European Medicines Agency Website in line with the latest QRD Template and to update the list of local representatives in the Package Leaflet (PL). Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/02/2010	30/03/2010	SmPC and PL	This variation based on pooled results from data acquired either during the course of clinical studies available since the vaccine registration in Europe or through post-marketing surveillance (PMS). A review of in total 23 completed clinical trials breaking down into 20 placebo-controlled and 3 non-placebo-controlled studies found additional previously unlisted adverse event (haematochezia) and that several frequency statements for listed adverse events needed to be revised. In addition, the PI was updated with information on cases of intussusception reported in temporal association with Rotarix in post-marketing experience. Most cases were reported within seven days following the first dose, however a clear causal relationship could not be established. Nevertheless, as a precaution, healthcare professionals should follow-up on any symptoms indicative

					of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever). Parents/guardians should be advised to promptly report such symptoms. Furthermore, a number of adverse events currently listed under section 4.8 of the SPC have been removed, as they are not considered to be plausibly causally related to Rotarix vaccination: upper respiratory tract infection, irritability, crying, sleep disorder, somnolence, hoarseness, rhinorrhoea, loss of appetite, vomiting, constipation, rash, muscle cramp, fever and fatigue. It could be demonstrated that there was no significant difference between the placebo and Rotarix groups concerning events which are considered related to rotavirus infection (fever, vomiting, irritability, loss of appetite). The PI was updated to reflect these findings.
II/0021	Change(s) to the manufacturing process for the finished product	21/01/2010	09/02/2010		
IA/0023	To add an alternative manufacturer for secondary packaging IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	21/01/2010	n/a		
II/0022	Change in cell identity method Change(s) to the test method(s) and/or specifications for the active substance	17/12/2009	04/01/2010		
II/0018	Update of sections 4.3, 4.4, and 4.8 of the SPC to include additional information on the safety and	23/07/2009	21/08/2009	SmPC and PL	The clinical study Rota-022 was conducted to evaluate the reactogenicity, safety and immunogenicity of 3 doses of

	immunogenicity of Rotarix when administered to HIV positive infants based on a clinical trial that evaluated reactogenicity, safety and immunogenicity of 3 doses of Rotarix given concomitantly with routine WHO Expanded Program on Immunization (EPI) vaccines including Oral Polio Vaccine (OPV) in asymptomatic or mildly symptomatic HIV positive infants. The PL was updated accordingly. In addition, sections 6.3 and 6.4 of the SPC were updated in line with the SPC Guideline and current guidance documents on storage conditions and to update the contact details for Cyprus and Slovenia in the list of local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet				Rotarix given concomitantly with routine WHO Expanded Program on Immunization (EPI) vaccines including Oral Polio Vaccine (OPV) in asymptomatic or mildly symptomatic (according to WHO classification) HIV positive infants in South Africa. The results suggested that 3 doses of Rotarix given concomitantly with routine childhood vaccines are as safe as 3 doses of placebo in HIV infected infants. The data obtained was considered sufficient to support the deletion of a contraindication for HIV positive subjects of the SPC and substituting this with a wording in section 4.4. The PL was updated accordingly to reflect the safety and immunogenicity changes of the SPC.
II/0017	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SPC regarding the Rotarix safety and immunogenicity when administered to pre-term infants with gestational age of 27 to 36 weeks based on a phase IIIb, double blind, randomised, placebo-controlled, multinational, multi-centre study to assess the safety, reactogenicity and immunogenicity of two doses of Rotarix in pre-term infants. The PL sections 2 and 3 are updated accordingly. In addition the MAH made minor changes to the Greek list of representatives. Paediatrics to validate	23/07/2009	21/08/2009	SmPC and PL	The SPC was updated with data from a phase III clinical study in Europe (Follow-Up Measure FUM 007, study Rota-054) to assess immunogenicity (in terms of anti-rotavirus (RV) IgA antibodies), as well as reactogenicity and safety of 2 doses of Rotarix in pre-term infants. To fulfil this commitment, study Rota-054 was conducted in 4 European countries to assess Rotarix safety when given to pre-term infants concomitantly with routine childhood vaccines. The efficacy and safety results from study Rota-054 showed that two doses of Rotarix may be given concomitantly with routine childhood vaccines in pre-term born at 27 to 36 weeks of gestation.

	Update of Summary of Product Characteristics and Package Leaflet				
II/0019	Change to the primary pack stopper and tip cap for pre-filled syringes. Change(s) to the manufacturing process for the finished product	25/06/2009	01/07/2009		
II/0016	Quality changes	19/03/2009	24/03/2009		
II/0015	Addition of a manufactoring facility for the secondary operation of filling and lyophilisation. Change(s) to the manufacturing process for the finished product	25/09/2008	01/10/2008		
X/0010	Annex I_2.(d) Change or addition of a new pharmaceutical form	26/06/2008	01/09/2008	SmPC, Labelling and PL	
II/0012	To update section 5.1 of the SPC with data from the second year follow-up of the study Rota 036 concerning vaccine efficacy in Europe. In addition, the MAH took the opportunity to correct a spelling error in SPC section 4.4 to include missing text in the class wording on apnoea and to amend SPC section 9 in compliance with the QRD templates. Update of Summary of Product Characteristics	30/05/2008	04/07/2008	SmPC	The SPC was updated with data from the second-year follow-up from a clinical study that evaluated the efficacy, immunogenicity, reactogenicity and safety of two doses of Rotarix in healthy infants when co-administered with specific childhood vaccinations in the European setting. The immunogenicity of childhood vaccinations was also evaluated to explore any effect of co-administration with the HRV vaccine. The efficacy results showed that sufficient protection against gastroenteritis caused by the serotypes G1P 8 , G2P 4 , G3P 8 , G4P 8 and G9P 8 continues in the second

					year of life, although the data for some of the serotypes indicate a certain waning immunity over time. No interference of Rotarix on immune response to antigens contained in coadministered childhood vaccines (Infanrix Hexa, Infanrix Polio Hib, Prevenar or Meningitec) could be observed in this study. The safety data for the second year was comparable with data from the first year in this study and did not raise any further concerns.
II/0013	To update section 4.5 of the SPC on concomitant administration of Rotarix with oral poliovirus vaccine based on data from a clinical study evaluating the concomitant use of Rotarix with routine WHO expanded program of immunisation (EPI) vaccinations in healthy infants. Update of Summary of Product Characteristics	24/04/2008	19/06/2008	SmPC	Based on a coadministration study of Rotarix with other vaccines, including oral polio vaccine (OPV), the wording of the SPC was updated to reflect that, although concomitant administration of OPV may slightly reduce the immune response to Rotarix, it was shown that the protection against severe rotavirus gastro-enteritis is maintained.
IA/0014	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	04/03/2008	n/a		
II/0011	Update of sections 4.4 "Special warnings and precautions for use" and 4.8 Undesirable effects" of the Summary of Product Characteristics to implement the class labelling text on the risk of apnoea following vaccination of very prematurely born infants agreed by the CHMP in July 2007. In addition, the MAH proposed to correct the "N" of Rotarix group and placebo group for the 1st year efficacy results in a table presenting the efficacy results of the study performed in Latin America in	15/11/2007	06/12/2007	SmPC and PL	Following a review on the risk of apnoea in very premature infants after immunisation the CHMP recommended a class labelling on apnoea for all vaccines in very premature infants. The SPC was updated to include information about the potential risk of apnoea and the need for respiratory monitoring for 48-72h, when the primary immunisation series is administered to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. Nonetheless, preterm infants should not be withdrawn from the

	section 5.1 of the SPC. Update of Summary of Product Characteristics and Package Leaflet				immunisation scheme because the benefit of vaccination outweighs the risk of apnoea.
II/0009	Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product	20/09/2007	25/09/2007		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/06/2007	n/a	Labelling and PL	
II/0007	Change(s) to the manufacturing process for the finished product	26/04/2007	07/05/2007		
II/0006	Change(s) to the manufacturing process for the finished product	24/01/2007	06/02/2007		
II/0005	Further to the review of the reports from post-marketing data the product information for Rotarix is updated to minimise the risk of maladministration. Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/10/2006	11/12/2006	SmPC, Labelling and PL	Following the review of all reports of parenteral administration of the oral vaccine Rotarix, the SPC, PL and labelling were updated in the view to minimise the risk of maladministration: For this purpose the term "vial" was replaced by "glass container", and the term "syringe" by "oral applicator". The pictograms have also been changed in order to make clear that the vaccine is for oral use. Furthermore, the term "oral" and the sentences "Do not inject" and "Rotarix should under no circumstances be injected" are highlighted in bold.

II/0001	To extend the therapeutic indication to include new information that efficacy against gastro-enteritis has also been demonstrated for rotavirus serotypes G4P[8], and G2P[4]. Extension of Indication	18/10/2006	11/12/2006	SmPC and PL	For further information please refer to the Scientific Discussion: EMEA-H-639-II-01-AR.
II/0004	Change(s) to the manufacturing process for the finished product	16/11/2006	30/11/2006		
IA/0003	IA_26_a_Change in the specification of immediate packaging - tightening of specification limits	04/09/2006	n/a		
IA/0002	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	04/09/2006	n/a		