Ixiaro

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/0108	A.7 - Administrative change - Deletion of manufacturing sites	19/03/2021		Annex II and PL	
IB/0106	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	29/01/2021	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).

	control/testing takes place				
IB/0105/G	This was an application for a group of variations. 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) 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.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.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	25/11/2020	n/a		
IB/0104	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	27/07/2020	n/a		
IB/0103	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure	06/04/2020	n/a		

	(including replacement or addition)				
IB/0102	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	29/01/2020	n/a		
IB/0101/G	This was an application for a group of variations. 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) 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) B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol	20/11/2019	10/03/2020	SmPC	
IA/0100/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 manufacturer of a novel excipient A.4 - Administrative change - Change in the name	30/08/2019	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				
IB/0099	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/08/2019	n/a		
IAIN/0098	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	12/04/2019	10/03/2020	Annex II and PL	
IB/0097/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.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	02/04/2019	10/03/2020	Annex II, Labelling and PL	
IB/0096	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/03/2019	n/a		
IB/0095	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	01/03/2019	n/a		

	of the AS				
R/0091	Renewal of the marketing authorisation.	20/09/2018	22/11/2018	SmPC, Annex II, Labelling and PL	
PSUSA/1801/ 201803	Periodic Safety Update EU Single assessment - japanese encephalitis virus (inactivated)	31/10/2018	n/a		PRAC Recommendation - maintenance
IB/0093/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.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.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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	17/10/2018	n/a		
IAIN/0094	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	18/09/2018	n/a		
IB/0092	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure	31/07/2018	n/a		

	(including replacement or addition)				
IA/0089	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	02/05/2018	n/a		
IB/0088/G	This was an application for a group of variations. B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	06/03/2018	n/a		
PSUSA/1801/ 201703	Periodic Safety Update EU Single assessment - japanese encephalitis virus (inactivated)	09/11/2017	08/01/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1801/201703.
IA/0087/G	This was an application for a group of variations. A.z - Administrative change - Other variation A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	14/12/2017	n/a		
IB/0086	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/06/2017	n/a		

IB/0084/G	This was an application for a group of variations. B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	31/05/2017	n/a		
II/0083	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	15/12/2016	n/a		
PSUSA/1801/ 201603	Periodic Safety Update EU Single assessment - japanese encephalitis virus (inactivated)	27/10/2016	n/a		PRAC Recommendation - maintenance
IB/0081/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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	22/06/2016	n/a		
II/0077	To change the in-process (Neutralised Inactivated Viral Solution (NIV)) and active Substance specifications with an ELISA testing method for the determination of antigen content:	26/05/2016	28/04/2017	SmPC, Annex II, Labelling and PL	The Final Vaccine Lot specifications have been changed and the protein stated in the product information, 6 µg/dose, has been replaced with 6 AU/dose (Antigen units/dose). Furthermore, the MAH took the opportunity to align the

	NIV Total Protein Content ≥ 15 µg/mL will be deleted Drug Substance Antigen Content ≥ 8 AU/mL to 8 - 18 AU/mL Drug Substance Total Protein Content 10-15 µg/mL to ≤ 20µg/mL Drug Substance Specific Activity 1.2 ± 0.6 AU/µg will be deleted Consequently, the Final Vaccine Lot specifications are changed and the protein stated in the SPC (6µg/dose) will be replaced with 6 AU/dose (Antigen units/dose): Antigen Content (calculated) N/A to 7.6 - 17.1 AU/mL Total Protein (calculated) 9.5 -14.2 µg/mL will be deleted Furthermore, the MAH took the opportunity to align the Product information with the latest QRD template version 10.0. 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				Product information with the latest QRD template version 10.0.
II/0075	Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update the immunogenicity and safety information and include recommendation on a booster dose in the paediatric population based on clinical trials IC51-322, IC51-324 and IC51-325. The Package Leaflet is updated accordingly. In addition,	01/04/2016	02/05/2016	SmPC, Labelling and PL	According to the presented antibody persistence and booster data, amendment of the Section 4.2 of the SmPC is proposed, i.e. recommendation of booster dose for children and adolescents. In support of this change, the Section 5.1 has been updated accordingly with inclusion of the immunogenicity data.

	the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0074	Update of sections 4.2 and 5.1 of the SmPC in order to include a recommendation for a second booster dose after 10 years and to update safety information based on results from study 311_FU2013 - an open-label, uncontrolled, multicenter, Phase 3 study that investigated the persistence of antibodies about 6 years after an IXIARO booster dose administered 15 months after the primary series. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	02/05/2016	SmPC, Annex II and PL	According to the presented persistence data up to 6 years after the first booster dose and a mathematic modelling the MAH included a recommendation for a second booster dose after 10 years in adults in the section 4.2 of the SmPC. In the SmPC section 5.1 the data of PRNT50 and the used mathematic modelling have been included.
IB/0080/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	20/04/2016	n/a		

	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				
IB/0079/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 manufacturer of a novel excipient 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	22/03/2016	n/a		
IA/0078	A.7 - Administrative change - Deletion of manufacturing sites	29/02/2016	n/a		
IB/0076	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	14/01/2016	n/a		
PSUSA/1801/ 201503	Periodic Safety Update EU Single assessment - japanese encephalitis virus (inactivated)	08/10/2015	n/a		PRAC Recommendation - maintenance

IB/0073	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	02/10/2015	n/a		
IB/0072/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.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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	10/09/2015	n/a		
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/09/2015	13/04/2016	PL	
IB/0070	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	17/08/2015	n/a		
IB/0069	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	13/07/2015	n/a		

IB/0067	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	08/05/2015	n/a		
II/0065/G	This was an application for a group of variations. C.I.4 Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to include data of the clinical study V49_23. C.I.z Update of section 4.2 to include relevant data on elderly population. The requested group of variations proposed changes to the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/04/2015	13/04/2016	SmPC and PL	
IB/0066/G	This was an application for a group of variations. 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) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	15/01/2015	n/a		

	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.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				
IB/0063/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.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	09/12/2014	n/a		
IB/0064	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	28/11/2014	n/a		
PSUV/0062	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IB/0061/G	This was an application for a group of variations.	08/08/2014	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.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) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0059	Changes 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	26/06/2014	n/a		
IB/0060	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	23/06/2014	n/a		
R/0055	Renewal of the marketing authorisation.	18/12/2013	28/02/2014	SmPC, Annex II and PL	IXIARO is an inactivated JE vaccine adsorbed to aluminium hydroxide (alum).

					It is the only vaccine indicated for active immunisation against Japanese encephalitis that is available in Europe and in the US. There is no specific (causally acting) therapy available for Japanese encephalitis infection. IXIARO has an established positive benefit risk profile shown both in clinical trials (high seroconversion rates, significant lack of serious adverse reactions) as well as in post-marketing (no confirmed cases of vaccination failure, limited number of serious reactions not affecting the safety profile). However, the post-marketing exposure of IXIARO to pediatric population is very small to date. This limited exposure, together with fewer than 2,000 pediatric subjects exposed in clinical trials, form a safety database that is too small to characterize rare or very rare adverse events, including the important identified and potential risks mentioned in the Risk Management Plan. Hence, the CHMP recommends one additional 5-year renewal of the Marketing Authorisation.
IAIN/0058/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	25/10/2013	28/02/2014	SmPC, Annex II, Labelling and PL	

IB/0057	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	02/09/2013	n/a		
IB/0056	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	21/08/2013	n/a		
IB/0054	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	15/08/2013	n/a		
IB/0053	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	29/07/2013	n/a		
T/0052	Transfer of Marketing Authorisation	03/05/2013	27/05/2013	SmPC, Labelling and PL	New Marketing Authorisation Holder: Intercell Austria AG Previous Marketing Authorisation Holder: Intercell AG
IB/0051/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	16/05/2013	n/a		

	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				
IB/0049	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	02/04/2013	n/a		
IB/0050	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	19/03/2013	n/a		
IB/0048/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.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	01/03/2013	n/a		
IB/0047	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	09/01/2013	n/a		

II/0039/G	This was an application for a group of variations. The MAH proposed the extension of indication of Ixiaro to the paediatric segment (2 months of age and older) in line with approved PIP EMEA -000559-PIP01-09-M03. Modification of syringe label to include "half dose mark" for administration of a 0.25 ml nominal dose for the paediatric sub-segment 2 months to below 3 years of age in line with the aforementioned PIP. The latter is grouped with the indication extension as direct result of the proposed extension. The Package Leaflet and Labelling were proposed to be updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 8.2. B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	13/12/2012	01/02/2013	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion in the Assessment Report: Ixiaro-H-963-II-0039-G-VAR-en
IB/0046	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	30/11/2012	n/a		
IB/0044	B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new	15/11/2012	n/a		

	specification parameter to the specification with its corresponding test method				
IB/0045	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	29/10/2012	n/a		
II/0042	to introduce a Post-approval change management protocol during the manufacture of the active substance. B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	18/10/2012	18/10/2012		
IB/0043	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	01/10/2012	n/a		
IB/0041	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	23/08/2012	n/a		
IB/0040/G	This was an application for a group of variations. 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	16/08/2012	n/a		

	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)				
IB/0038/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.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	31/05/2012	n/a		
A20/0029	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 01 June 2011, the opinion of the CHMP on measures necessary to ensure the safe and effective use of the above mentioned medicinal product further to the CHMP review on the impact of the out-of-specification result observed for one batch of the product.	15/03/2012	25/05/2012	Annex II	Please refer to Assessment Report: Ixiaro-H-C-963-A20-0029
IB/0037	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing	12/04/2012	n/a		

	takes place				
IB/0036	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	13/03/2012	n/a		
IB/0035	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	08/03/2012	n/a		
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/02/2012	25/05/2012	PL	
IB/0034	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	09/01/2012	n/a		
II/0030	To add a working cell bank to the production of Ixiaro 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	22/09/2011	22/09/2011		
IB/0031/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.I.b.2.e - Change in test procedure for AS or	16/09/2011	n/a		

	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)				
IB/0028/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/07/2011	n/a		
IB/0026/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including	17/06/2011	n/a		

	replacement or addition) 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/0023	to introduce a second working virus seed bank . B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	19/05/2011	19/05/2011		
IB/0027/G	This was an application for a group of variations. 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)	16/05/2011	n/a		
IA/0024/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance	02/05/2011	n/a		

	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) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0022/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	05/04/2011	n/a		
IB/0021/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	05/04/2011	n/a		
IB/0020	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	28/03/2011	n/a		

N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/03/2011	n/a	PL	
IB/0019/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.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	03/02/2011	n/a		
II/0016	To revise the in-process acceptance criteria in the manufacture of the active substance. B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	16/12/2010	04/01/2011		
IB/0017/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	14/12/2010	n/a		

	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				
IB/0015	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	29/11/2010	n/a		
IB/0013/G	This was an application for a group of variations. 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)	29/11/2010	n/a		
IB/0014/G	This was an application for a group of variations. B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	25/11/2010	n/a	SmPC	

II/0011/G	This was an application for a group of variations. To replace testing methodology of determining the degree of adsorption for Drug Product and to tighten the specification of degree of adsorption for Drug Product. B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue	22/07/2010	16/08/2010		
IA/0012	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)	16/07/2010	n/a		
II/0008	Replacement of a test for bacterial endotoxins for incoming raw material. B.II.c.2.c - Change in test procedure for an excipient - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	20/05/2010	03/06/2010		

II/0007	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	22/04/2010	04/05/2010		
II/0006/G	This was an application for a group of variations. 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 B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	22/04/2010	03/05/2010		
IB/0010/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.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	29/04/2010	n/a		

IB/0009/G	This was an application for a group of variations. 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)	22/04/2010	n/a		
II/0005	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SPC based on the 24 and 36 months immunogenicity and safety data from studies IC51-303, -305, and -311 in line with follow-up measures 016 and 018. The PL was updated accordingly. The MAH also took this opportunity to add the approved EU numbers in section 8 of the SPC and to amend the instructions for disposal in section 6.6 of the SPC. Furthermore, the MAH took this opportunity to correct a minor spelling mistake in the address of the manufacturer in Annex II and to update the European Medicines Agency web site address. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	23/03/2010	SmPC, Annex II and PL	The data demonstrate that for the antibody response following primary immunisation regimen of 2x 6µg is long-lasting and clearly boosterable after 11 or 23 months. This is further corroborated by immunogenicity data on a booster dose given 15 months after the primary immunisation. Therefore, subjects with a continuously high risk of exposure to Japanese encephalitis should receive a booster dose within a time interval of 1 to 2 years after the primary immunisation series to ensure optimal protection. Moreover the data indicate that subjects, who received only a single dose of 1x 6µg respond effectively to a booster dose given 11 months after the first dose. This information is deemed to be important for travellers which are in urgent need to be at least partly protected within a short time frame and are not able to complete the primary immunisation series (e.g. last minute travellers). In addition the list of adverse events was updated to reflect the safety data from the studies submitted.

II/0002	The MAH applied to extend the Shelf life of Ixiaro from 12 months to 18 months. Quality changes	24/09/2009	28/10/2009	SmPC and PL	
II/0001	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to version 7.0 as a consequence of the FUMS 0016 (24 months reports from clinical studies IC51-303 and IC51-305) and to reflect updated processes. The Risk Management Plan (RMP) has also been updated to version 1.4. Consequently, Annex II has been updated with the new version numbers of the agreed DDPS and RMP. Update of DDPS (Pharmacovigilance)	24/09/2009	28/10/2009	Annex II	The Detailed Description of the Pharmacovigilance System and Risk Management Plan (RMP) have been updated. The DDPS has been amended in its structure and organisation, inclusion of trials with long-term observations and post-marketing surveillance program, update on the processing of pharmacovigilance data from post-marketing surveillance studies and also few technical changes were included. Consequently, Annex II.B has been updated using the standard text including the new version number of the agreed DDPS and RMP.
II/0004	Introduction of an internal reference material for the testing of drug substance and drug product. Quality changes	24/09/2009	05/10/2009		
II/0003	The MAH applied for changes in the testing methodology of the Drug Substance. Quality changes	24/09/2009	05/10/2009		