ReFacto AF

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
N/0166	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2022		Labelling and PL	
IB/0164/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other	27/09/2022	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).

	variation B.II.z - Quality change - Finished product - Other variation				
II/0163/G	This was an application for a group of variations. B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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.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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters	05/05/2022		Annex II	The Annex II has been updated by adding Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, Ireland as an alternative site responsible for manufacture of the active substance moroctocog alfa.

	and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch				

	control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product				
N/0162	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/09/2021		PL	
IB/0161/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 starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	17/08/2021	n/a		
II/0158/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.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.e - Change in the specification parameters	15/07/2021	n/a		

	and/or limits of the finished product - Change outside the approved specifications limits range				
IB/0160	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	12/07/2021	n/a		
IA/0159	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	19/04/2021	n/a		
PSUSA/2089/ 202008	Periodic Safety Update EU Single assessment - moroctocog alfa	09/04/2021	n/a		PRAC Recommendation - maintenance
IB/0156	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	07/12/2020	n/a		
IB/0155	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/10/2020	11/10/2021	SmPC, Annex II and PL	
IB/0154/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other variation B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	10/09/2020	n/a		

	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.z. - Change in supplier of packaging components or devices (when mentioned in the dossier) - Other variation B.II.e.7.z. - Change in supplier of packaging components or devices (when mentioned in the dossier) - Other variation				
II/0153/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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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.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	23/07/2020	n/a		

	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.g.3 - Deletion of an approved change management protocol related to the finished product				
II/0151	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/09/2019	30/09/2020	SmPC	
IB/0152/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 sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products 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 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	01/08/2019	n/a		

PSUSA/2089/201808	Periodic Safety Update EU Single assessment - moroctocog alfa	11/04/2019	n/a		PRAC Recommendation - maintenance
IA/0150/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	14/02/2019	n/a		
IA/0149	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	18/12/2018	n/a		
II/0147	Submission of the final report from study B1831007 (previously referred to as Study 3082B2-4435-WW) listed as a category 3 study in the RMP. This is a post authorisation safety surveillance registry in previously untreated patients with severe haemophilia A in usual care settings, in order to fulfil the post-approval commitment MEA 115. C.I.13 - Other variations not specifically covered	04/10/2018	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
T/0146	Transfer of Marketing Authorisation	11/07/2018	02/08/2018	SmPC, Labelling and PL	
IB/0145	B.II.z - Quality change - Finished product - Other variation	02/07/2018	n/a		
II/0143	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2018	02/08/2018	SmPC, Labelling and PL	
II/0142	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/01/2018	n/a		
IA/0144	A.7 - Administrative change - Deletion of manufacturing sites	08/12/2017	n/a		
A31/0134	Pursuant to Article 31 of Directive 2001/83/EC, Germany initiated a procedure on 6 July 2016 based on concerns resulting from the evaluation of data from pharmacovigilance activities. The PRAC was requested to assess the potential impact of the results of the SIPPET study (which concluded that recombinant factor VIII medicines had a higher incidence of inhibitor development than plasma-derived medicines), and to issue a recommendation as to whether the marketing authorisations of these products should be	14/09/2017	15/11/2017	SmPC and PL	Please refer to the assessment report: human coagulation factor VIII - EMEA/H/A-31/1448

	maintained, varied, suspended or revoked. The EMA concluded in September 2017 that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: those derived from plasma and those made by recombinant DNA technology. Due to the different characteristics of individual products within the two classes, EMA concluded that the risk of inhibitor development should be evaluated individually for each medicine, regardless of class. The risk for each product will continue to be assessed as more evidence becomes available.				
II/0140	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/11/2017	n/a		
IA/0141	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	18/08/2017	n/a		
II/0139	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	18/05/2017	n/a		
PSUSA/2089/ 201608	Periodic Safety Update EU Single assessment - moroctocog alfa	06/04/2017	n/a		PRAC Recommendation - maintenance

IB/0138	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/12/2016	n/a		
IB/0136	To include the certification of the alcohol swab and the sterile gauze as Medical Devices components. In addition the MAH took the opportunity to remove Medimop 510 k certificate from the regional information since this certification is not required in the European markets. B.IV.z - Quality change - Change in Medical Devices - Other variation	25/11/2016	n/a		
II/0131	Update of section 4.2 of the SmPC regarding use in the elderly, and section 4.8 of the SmPC to reflect revised frequency categories of listed ADRs, as applicable, in line with the MAH's updated CDS based on all-causality treatment-emergent AEs from a pooled dataset from 7 clinical studies. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, to consolidate the nine SmPCs for the two different presentations into one combined SmPC, to align the annexes with the latest QRD templates version 9.1 and the revised Core FVIII SmPC, and to update the contact details of the local representatives in the Czech Republic, Norway and Sweden in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to	23/06/2016	29/07/2016	SmPC, Annex II and PL	Clinical studies did not include subjects aged 65 and over. In general, dose selection for an elderly patient should be individualised.

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0133/G	This was an application for a group of variations. 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.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/06/2016	29/07/2016	Labelling	
II/0132/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.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.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	14/04/2016	n/a		
IA/0130	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	20/11/2015	n/a		
IB/0129	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change	21/10/2015	n/a		

	in the manufacturing process				
II/0127/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation 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	n/a		
N/0126	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/08/2015	29/07/2016	Labelling	
IA/0128	A.7 - Administrative change - Deletion of manufacturing sites	28/07/2015	n/a		
N/0125	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	29/07/2016	PL	
PSUSA/2089/ 201408	Periodic Safety Update EU Single assessment - moroctocog alfa	12/03/2015	n/a		PRAC Recommendation - maintenance
II/0122	B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	25/09/2014	n/a		
IA/0123/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary)	17/09/2014	n/a		

	packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
IB/0121	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	29/04/2014	n/a		
II/0120	Update of sections 4.8 and 5.1 of the SmPC in order to include data on immune tolerance induction (ITI) with ReFacto in line with the reflection paper on ITI in haemophilia A patients who had developed inhibitors to factor VIII. In addition, the MAH took the opportunity of this variation to make editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	08/04/2015	SmPC	As part of the study 3082A1-301-WW investigating the immediate and long-term safety and efficacy of ReFacto (moroctocog alfa) in PUPs, data on immune tolerance induction from 25 patients with haemophilia A who had developed inhibitors to factor VIII were reviewed. Of these 25 patients, 20 had a decrease in inhibitor titres to <0.6 BU, of whom initially 11 of 15 had high titres (≥5 BU) and 9 of 10 had low titres. Out of 6 patients who developed low titre inhibitors but did not receive ITI, 5 had similar titre decreases.
PSUV/0118	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
II/0119/G	This was an application for a group of variations.	20/02/2014	n/a		

	B.I.a.1.e - Introduction of an additional site for Working Cell Banks preparation; B.I.a.1.k - Indroduction of a new sorage site for Master Cell Banks and Working Cell Banks; A.4 - Change in the name of a manufacturing site. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB 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				
II/0117	Submission of the final clinical study report of study 3082B2-4432-WW (B1831004) 'A post-authorisation safety surveillance study of patients switching to ReFacto AF from ReFacto or other Factor VIII products in usual care settings'. No changes to the product information are proposed. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2013	n/a		The MAH submitted the final study report of study 3082B2-4432-WW (B1831004) 'A post-authorisation safety surveillance study of patients switching to ReFacto AF from ReFacto or other Factor VIII products in usual care settings'. The report includes results from 208 patients that were enrolled into the study. There were no occurrences of clinically significant FVIII inhibitor development during this study. No new safety risks or concerns for previously treated patients administered ReFacto AF after switching from ReFacto or other FVIII products in the usual care

					setting have been identified.
R/0115	Renewal of the marketing authorisation.	19/09/2013	13/11/2013	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Refacto AF continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
N/0116	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2013	13/11/2013	PL	
IB/0114/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)	25/06/2013	n/a		
IA/0113	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	17/04/2013	n/a		
IA/0112	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement	07/12/2012	n/a		

	or addition of a site where batch control/testing takes place				
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
II/0109	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products	20/09/2012	24/10/2012	SmPC, Annex II, Labelling and PL	Currently the following strengths of ReFacto AF are approved: 250 IU, 500 IU, 1000 IU and 3000 IU (3000 IU was approved by EMEA/H/C232/X/87 in May 2011). A dual-chamber pre-filled syringe was introduced by procedure EMEA/H/C/232/X/90 (May 2011), for the strengths 500 IU, 1000 IU and 3000 IU. By this variation the Applicants apply for the introduction of the 250 IU strengths also to be available as a dual-chamber presentation. The 250 IU ReFacto AF syringe is manufactured using the same drug substance that is used to formulate current ReFacto AF product in vials.
II/0102	Update of section 4.8 of the SmPC in order to include safety data from clinical study 3082B2-311 which evaluated moroctocog alfa (AF-CC) for surgical prophylaxis in previously treated patients with severe or moderately severe disease (FVIII:C<2%) haemophilia A. The Package Leaflet has been updated in accordance. In addition, the conditions or restrictions with regard	19/07/2012	30/08/2012	SmPC and PL	Final results of Study 3082B2-311 evaluating moroctocog alfa (AF-CC) for surgical prophylaxis in PTPs with severe or moderately severe disease have been submitted. Data from this study have been pooled with data from 3 completed studies of moroctocog alfa (AF_CC) (Studies 3082B2-310, 3082B1-306 and 3082B1-307) and 2 studies from moroctocog alfa (Studies 3082A1-300 and 3082A1-301) to update the incidence of adverse drug reactions (ADRs)

	to the safe and effective use of the medicinal product have been deleted further to the CHMP request made during the assessment of PSUR 133. The MAH took the opportunity to bring the PI in line with the latest version of the QRD template (version 8.1) and introduce some minor editorial changes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				observed in clinical studies. These data form the basis for update of section 4.8 of the SmPC.
IB/0110	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	07/08/2012	n/a		
IB/0106	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	26/06/2012	30/08/2012	SmPC and Annex II	
IG/0169/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	08/06/2012	n/a		

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0105	A.7 - Administrative change - Deletion of manufacturing sites	24/05/2012	n/a		
IB/0104	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	18/05/2012	n/a		
II/0103	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	19/04/2012	n/a		
II/0100	Change in the batch size of the active substance B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	16/02/2012	16/02/2012		
IB/0101	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	09/12/2011	n/a		
IA/0099	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/09/2011	n/a		

IB/0096	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	20/09/2011	n/a		
IB/0095	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	15/09/2011	n/a		
IA/0098	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/09/2011	n/a		
IA/0097	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	05/09/2011	n/a	Annex II	
IA/0094	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/08/2011	n/a		
T/0093	Transfer of Marketing Authorisation	24/06/2011	18/07/2011	SmPC, Labelling and PL	
WS/0117	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	14/04/2011	23/05/2011	Annex II	

X/0090	Extension of the Application to include 500, 1000 and 2000 IU powder and solvent for solution for injection in pre-filled syringe. Annex I_2.(d) Change or addition of a new pharmaceutical form	17/02/2011	06/05/2011	SmPC, Annex II, Labelling and PL	The MAH applied for a dural-chamber pre-filled syringe to facilitate patients reducing the number of steps and components necessary to reconstitute the finished product. The finished product is ready to be administered to the pateints after performing one reconsitution step through the use of the self contained dual-chamber glass syringe.
X/0087	To apply for a new 3000 IU presentation. Annex I_2.(d) Change or addition of a new pharmaceutical form	17/02/2011	06/05/2011	SmPC, Annex II, Labelling and PL	
N/0092	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2010	n/a	Labelling	
N/0091	The MAH has applied to update the details of the local representatives in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2010	n/a	PL	
IB/0089	B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	30/07/2010	n/a		
IA/0088	To change the specifications of Tri-butyl phosphate (TNPB) to comply with the Ph. Eur.	18/06/2010	n/a		

	B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
IB/0086	To add an intermediate condition of 30 ± 2°C/65 ± 5% RH in the satbility protocol for future long term stability studies for 0.9% NaCl diluent prefilled syringe. B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	20/05/2010	n/a		
IB/0084	To extend the shelf life of the 0.9% NaCl diluent prefilled syringe from 36 months to 60 months. 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)	20/05/2010	n/a		
IB/0083	To extend the shelf life of the finished product from 24 months to 36 months. 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	20/05/2010	n/a	SmPC	
IA/0085	To amend the release specification for 0.9% NaCl	23/04/2010	n/a		

	diluent pre-filled syringe from "Clear, colorless solution" to "Clear, colorless solution practically free from particulates", which is required by Ph. Eur. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits				
IA/0082	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	14/04/2010	n/a	Annex II	
IA/0081	C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities	14/04/2010	n/a	Annex II	
IA/0080	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	14/04/2010	n/a	Annex II	
IA/0079	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	14/04/2010	n/a	Annex II	
IA/0078	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	14/04/2010	n/a	Annex II	

N/0077	Change in cell identity method. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/03/2010	n/a	PL	
IA/0076	IA_09_Deletion of manufacturing site	10/07/2009	n/a	Annex II and PL	
IA/0075	IA_05_Change in the name and/or address of a manufacturer of the finished product	10/07/2009	n/a	Annex II and PL	
II/0074	Changes to QPPV Update of DDPS (Pharmacovigilance)	29/05/2009	01/07/2009	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS) [Module 1.8.1] to reflect a change in the Qualified Person in the EEA for Pharmacovigilance (QPPV). Other administrative and editorial changes are incorporated in this revised DDPS (version 2.1).
II/0073	To introduce an alternate laboratory for release and shelf-life sterility testing of the ReFacto AF drug product. Furthermore, in section 3.2.P.3.3. minor change has also been introduced. Quality changes	23/04/2009	27/04/2009		
R/0072	Renewal of the marketing authorisation.	19/02/2009	16/04/2009	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 Refacto AF remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

					- to ensure appropriate monitoring of the introduction of the new Refacto AF on the market - to ensure appropriate implementation of the pharmacovigilance system / risk management plan The CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required.
II/0068	To change the manufacturing process of the active substance to an albumin free cell culture process and several consequential changes. These consist of 1. Minor changes in the purification process, 2. Drug substance specification changes 3. Drug substance HCP assay changes, These changes also result in the need for risk minimisation activities as set out in the agreed Risk Management Plan. The Annexes have been updated with additional ReFacto (AF-CC) data and to reflect the changes in the name (consequential but separate type I variation (EMEA/H/C/232/IB/70)) and the manufacturing process (no human or animal derived protein in the cell culture process). Wyeth has also taken this opportunity to update the Annexes into QRD template v7.2 and in line with recent Readability Testing for our Factor IX product. Change(s) to the manufacturing process for the active substance	18/12/2008	26/02/2009	SmPC, Annex II, Labelling and PL	Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.

II/0066	Change the potency standard calibration against the 7th IS. Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	18/12/2008	26/02/2009	SmPC, Labelling and PL	Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.
II/0067	A change in the container closure system of the Drug Product. Change(s) to the manufacturing process for the finished product	18/12/2008	12/01/2009		Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.
II/0065	Drug substance and drug product assay changes Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	18/12/2008	12/01/2009		Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.
II/0064	A change in the finished product. Change(s) to the manufacturing process for the finished product	18/12/2008	12/01/2009		Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.
II/0063	To change the finished product and stability specifications. Change(s) to the test method(s) and/or specifications for the finished product	18/12/2008	12/01/2009		Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.

II/0062	Change of manufacturing process for finished product. Change(s) to the manufacturing process for the finished product	18/12/2008	12/01/2009		Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.
II/0061	To increase the batch size of the finished product for the 2000IU strength. Change(s) to the manufacturing process for the finished product	18/12/2008	12/01/2009		Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.
II/0060	Introduction of filter in the drug substance manufacturing process. Change(s) to the manufacturing process for the active substance	18/12/2008	12/01/2009		Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.
II/0059	Change in the manufacturing process of the active substance purification Change(s) to the manufacturing process for the active substance	18/12/2008	12/01/2009		Please refer to the Scientific discussion: ReFacto AF-H-232-II-59-68-AR.
IB/0070	IB_02_Change in the name of the medicinal product	18/12/2008	n/a	SmPC, Labelling and PL	
IB/0071	IB_17_b_Change in the storage conditions for the active substance	12/11/2008	n/a		

II/0069	Change(s) to the manufacturing process for the finished product	18/10/2007	24/10/2007		
II/0057	Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	
IA/0056	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	05/03/2007	n/a		
II/0051	This variation is to transfer a manufacturing area for the drug substance in one of the current approved facilities. Quality changes	18/09/2006	20/10/2006		
IA/0055	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	05/07/2006	n/a	Annex II and PL	
II/0050	Quality changes	28/06/2006	03/07/2006		
IA/0054	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	28/06/2006	n/a		
IA/0053	IA_09_Deletion of manufacturing site	28/06/2006	n/a		
IB/0052	IB_30_b_Change in supplier of packaging components - replacement/addition	26/06/2006	n/a		
II/0049	Change(s) to the manufacturing process for the finished product	01/06/2006	07/06/2006		

II/0048	Quality changes	26/01/2006	31/01/2006		
II/0047	Change(s) to the manufacturing process for the active substance	26/01/2006	31/01/2006		
II/0046	Quality changes	26/01/2006	31/01/2006		
IB/0045	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	08/11/2005	n/a		
II/0044	The MAH has applied to amend the SPC, PIL in accordance with the Company Core Data Sheet (version 6), on the basis on two completed clinical trials. As a result, sections 4.2, 4.3, 4.8, 5.2 of the SPC and 6.6 have been updated. In addition, editorial changes of the labelling are proposed. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/06/2005	27/07/2005	SmPC, Labelling and PL	The MAH has applied to amend the SPC, PIL in accordance with the Company Core Data Sheet (version 6), on the basis on two completed clinical trials. As a result, sections 4.2, 4.3, 4.8, 5.2 of the SPC and 6.6 have been updated. In addition, editorial changes of the labelling are proposed.
IA/0043	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/02/2005	n/a	Annex II and PL	
II/0042	Quality changes	21/10/2004	25/11/2004	SmPC, Labelling and PL	The Marketing Authorisation Holder applied for a reversion from the current 36-months expiry period back to the original 24-months expiry period for all dosage strengths, maintaining the 3 months at 25°C during the 24-month time period.
II/0037	The Marketing Authorisation Holder applies for a modification of the ReFacto kit by introducing two new components, pre-filled diluent syringe and	03/06/2004	29/07/2004	SmPC, Labelling and	The Marketing Authorisation Holder applies for a modification of the ReFacto kit by introducing two new components, pre-filled diluent syringe and external

	external reconstitution device. Change(s) to container			PL	reconstitution device.
R/0038	Renewal of the marketing authorisation.	24/03/2004	20/07/2004	PL	
II/0039	The Marketing Authorisation Holder applies for the introduction of an additional assay to the drug substance specification. Change(s) to the test method(s) and/or specifications for the active substance	24/03/2004	31/03/2004		
IA/0041	IA_09_Deletion of manufacturing site	18/03/2004	n/a		
IB/0040	IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	15/03/2004	n/a		
II/0032	Quality changes	20/11/2003	16/12/2003		
I/0033	Change(s) to shelf-life or storage conditions	20/11/2003	n/a		
IB/0036	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	30/10/2003	n/a	SmPC	
II/0034	Update of or change(s) to the pharmaceutical documentation	22/10/2003	23/10/2003		
I/0030	12_Minor change of manufacturing process of the active substance	25/09/2003	02/10/2003		

I/0035	20a_Extension of shelf-life or retest period of the active substance	22/09/2003	23/09/2003		
I/0029	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process 11a_Change in the name of a manufacturer of the active substance	18/07/2003	22/07/2003		
T/0028	Transfer of Marketing Authorisation	02/05/2003	15/05/2003	SmPC, Labelling and PL	
II/0026	Quality changes	20/02/2003	08/05/2003	SmPC	
II/0027	Change(s) to the test method(s) and/or specifications for the active substance	20/03/2003	26/03/2003		
X/0022	X-3-iii_Addition of new strength	19/09/2002	19/12/2002	SmPC, Annex II, Labelling and PL	
II/0023	Change(s) to the manufacturing process for the finished product	21/11/2002	10/12/2002		
II/0024	Update of or change(s) to the pharmaceutical documentation	17/10/2002	21/10/2002		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/08/2002	18/09/2002	PL	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	25/04/2002	20/08/2002	SmPC and PL	

II/0014	Update of Summary of Product Characteristics	21/02/2002	25/06/2002	SmPC	
II/0021	Change(s) to container	25/04/2002	29/04/2002		
I/0020	01_Change in the name of a manufacturer of the medicinal product 11a_Change in the name of a manufacturer of the active substance	29/01/2002	28/02/2002	Annex II	
II/0013	Quality changes	17/01/2002	23/01/2002		
II/0012	Quality changes	17/01/2002	23/01/2002		
II/0010	Change(s) to the test method(s) and/or specifications for the active substance	18/10/2001	31/10/2001		
I/0016	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	29/10/2001	n/a		
II/0009	Update of or change(s) to the pharmaceutical documentation	23/08/2001	03/09/2001		
I/0008	30_Change in pack size for a medicinal product	12/12/2000	23/02/2001	SmPC, Labelling and PL	
I/0007	03_Change in the name and/or address of the marketing authorisation holder	06/10/2000	27/12/2000	SmPC, Labelling and PL	

I/0006	01_Change following modification(s) of the manufacturing authorisation(s)	27/06/2000	11/08/2000	Annex II and PL	
I/0004	14_Change in specifications of active substance	16/02/2000	01/03/2000		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/02/2000	06/04/2000	Labelling and PL	
I/0003	04_Replacement of an excipient with a comparable excipient	18/10/1999	21/10/1999		
I/0001	12_Minor change of manufacturing process of the active substance	20/10/1999	21/10/1999		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/10/1999	31/01/2000	Labelling and PL	