EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Arzerra

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/0052	A.7 - Administrative change - Deletion of manufacturing sites	27/07/2017	n/a		
II/0051	Update to sections 4.6 and 5.3 of the SmPC based on a cumulative review of data from completed non-clinical safety studies, cases reported in the pharmacovigilance database related to pregnancy and foetal exposure while receiving ofatumumab therapy.	20/07/2017		SmPC, Annex II, Labelling and PL	Since ofatumumab may cause foetal B-cell depletion, effective contraception (methods that result in less than 1% pregnancy rates) has to be used during Arzerra therapy and for 12 months after the last Arzerra dose. At the end of organogenesis (day 48 of gestation), the ofatumumab exposure (AUCinf) corresponded to 0.46 to 3.6 times the

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	Update to the section 4.5 of the SmPC based on results from clinical study OMB11360 investigating pharmacokinetic interactions between ofatumumab and bendamustine. Updates to sections 4.2, 5.1 and 5.2 of the SmPC were made to simplify them and ease their understanding. Editorial updates were made to sections 4.4 and 4.8. Furthermore, the MAH took the opportunity to combine the SmPCs of the different strengths (100 mg and 1000 mg concentrate for solution for infusion), to introduce editorial changes and to bring the PI in line with the latest QRD template version 10. In addition, the list of local representatives in the Package Leaflet has been updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				human exposure after the eighth infusion of the maximum recommended human dose (MRHD) of 2000 mg. Ofatumumab may cause foetal B-cell depletion based on findings from animal studies and on its mechanism of action. There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. No teratogenicity or maternal toxicity were observed in an animal reproduction study with administration of ofatumumab to pregnant monkeys. Administration of live vaccines to neonates and infants exposed to ofatumumab in utero should be avoided until B-cell recovery occurs. The preclinical safety section 5.3 of the SmPC was updated to reflect data on embryofoetal development in cynomolgus monkeys. Results from clinical study OMB157D2101 (OMB113603) showed no clinically relevant pharmacokinetic interactions between ofatumumab and bendamustine.
II/0050	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add a recommendation to permanently discontinue Arzerra in case of anaphylactic reaction and revise the adverse drug reaction profile based on cumulative safety pool data analysis from clinical trials, the company safety database and updated company core data sheet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017		SmPC and PL	Arzerra should be immediately and permanently discontinued in patients who develop an anaphylactic reaction to the medicinal product and appropriate medical treatment should be initiated. Section 4.8 has been revised to update the adverse drug reaction profile: to add “progressive multifocal leukoencephalopathy” with frequency “uncommon”. As a serious condition, progressive multifocal leukoencephalopathy is already included in the ‘Special warnings and precautions for use’ Section of the SmPC. The following adverse drug reactions were also added: “headache” and “infusion-related reactions” with frequency

					"common", and to additionally update the frequency of other adverse reactions.
PSUSA/2202/ 201610	Periodic Safety Update EU Single assessment - ofatumumab	05/05/2017	n/a		PRAC Recommendation - maintenance
II/0048	Submission of final clinical study of the study OMB115991: A Phase II, Multi-Centre Study Investigating the Safety and Efficacy of Ofatumumab Plus Bendamustine in Patients with Untreated or Relapsed CLL. is recommended for approval. The variation leads to no amendments to the Product Information. 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		
II/0045/G	This was an application for a group of variations. Extension of indication to include the combination of Arzerra with fludarabine and cyclophosphamide for the treatment of adult patients with relapsed Chronic Lymphocytic Leukaemia; as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 and 9 of the SmPC are updated based on the analysis of the pivotal study OMB110913 (COMPLEMENT 2). The Package Leaflet and Risk Management Plan (v.13.1) are updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) -	10/11/2016	08/12/2016	SmPC and PL	Please refer to the Scientific Discussion Arzerra II-45.

	Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0047/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.7 - Administrative change - Deletion of manufacturing sites	15/09/2016	n/a		
PSUSA/2202/ 201510	Periodic Safety Update EU Single assessment - ofatumumab	13/05/2016	n/a		PRAC Recommendation - maintenance
IAIN/0046/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	11/05/2016	n/a		

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II/0043	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	18/02/2016	06/07/2016	Annex II	
IB/0042	B.I.z - Quality change - Active substance - Other variation	11/11/2015	n/a		
PSUSA/2202/201504	Periodic Safety Update EU Single assessment - ofatumumab	06/11/2015	n/a		PRAC Recommendation - maintenance
IAIN/0039/G	This was an application for a group of variations. 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	13/07/2015	06/07/2016	Annex II and PL	

	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				
PSUSA/2202/ 201410	Periodic Safety Update EU Single assessment - ofatumumab	07/05/2015	n/a		PRAC Recommendation - maintenance
T/0038	Transfer of Marketing Authorisation from Glaxo Group Ltd. to Novartis Europharm Limited. Transfer of Marketing Authorisation	24/04/2015	06/05/2015	SmPC, Labelling and PL	
II/0035	Submission of a study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine refractory CLL to address the outstanding specific obligation of the conditional MA. As a consequence to the submission of the studies set in Annex II, the status of the MA changes from conditional to an MA not subject to specific obligations. The SmPC was revised accordingly. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	26/02/2015	24/04/2015	SmPC, Annex II and PL	

IB/0037	To add BioReliance Corporation, 9900 Blackwell Road, Rockville, Maryland, 20850 US as an alternative site responsible for quality control testing (in vitro viruses and mycoplasma tests) of the active substance. 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	08/04/2015	n/a		
R/0033	Renewal of the marketing authorisation.	18/12/2014	17/02/2015		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Arzerra, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IB/0034	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	20/11/2014	n/a		
PSUV/0030	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IB/0032	To extend the timeline from 31 December 2014 to 30 November 2015 for the Annex II condition ANX 007 for the further investigation of the effect of chromosome abnormalities on progression-free survival and overall survival. In addition the Greek	30/10/2014	17/02/2015	Annex II	

	SmPC, section 4.2 has been amended due to an error. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IA/0031/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	12/08/2014	n/a		
II/0027	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	28/07/2014	SmPC and PL	Intravenous ofatumumab has been associated with infusion reactions. These reactions may result in temporary interruption or withdrawal of treatment. Pre-medications attenuate infusion reactions but these may still occur, predominantly during the first infusion. Infusion reactions may include, but are not limited to, anaphylactoid events, bronchospasm, cardiac events (eg. myocardial ischaemia / infarction, bradycardia), chills/rigors, cough, cytokine release syndrome, diarrhoea, dyspnoea, fatigue, flushing, hypertension, hypotension, nausea, pain, pulmonary oedema, pruritus, pyrexia, rash, and urticaria. In rare cases, these reactions may lead to death. Even with pre-medication, severe reactions, including cytokine release syndrome, have been reported following use of ofatumumab. In cases of severe infusion reaction, the infusion of Arzerra must be interrupted immediately and

					symptomatic treatment instituted Patients should be closely monitored during administration of ofatumumab for the onset of infusion reactions, including cytokine release syndrome, particularly during the first infusion. Patients should always be pre-medicated 30 minutes to 2 hours prior to Arzerra infusion according to the dosing schedules described in section 4.2 of the SmPC.
IB/0029	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	03/07/2014	n/a		
II/0023	Extension of Indication to include in previously untreated chronic lymphocytic leukaemia (CLL) patients, the treatment in combination with chlorambucil or bendamustine of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy. As a consequence, sections 2, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/05/2014	30/06/2014	SmPC and PL	Please refer to the Scientific Discussion Arzerra EMEA/H/C/001131/II/0023.
IAIN/0028	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	13/06/2014	28/07/2014	SmPC, Labelling and PL	

PSUV/0026	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
II/0021	Update of section 4.4 of the SmPC in order to update the warning of Hepatitis B reactivation and of section 4.8 of the SmPC in order to add the adverse reaction of Hepatitis B infection and reactivation with a frequency rare, following a review of relevant cases from the MAH's worldwide clinical safety database and the scientific literature. The Package Leaflet is updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.0 and the contact details of the Croatian local representative are added in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	16/01/2014	SmPC, Annex II and PL	Following cases of HBV infection and reactivation in patients treated with anti-CD20 monoclonal antibodies, it is now recommended that all patients should be screened for HBV infection before starting treatment with ofatumumab. Patients with active/current hepatitis B infection should not be treated with ofatumumab. For patients with positive hepatitis B serology (but no active/current disease), a liver disease expert should be consulted regarding monitoring and initiation of HBV antiviral therapy. In patients who develop reactivation of HBV while receiving ofatumumab, ofatumumab and any concomitant chemotherapy should be interrupted immediately, and appropriate treatment instituted.
R/0018	Renewal of the marketing authorisation.	21/11/2013	16/01/2014	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Arzerra, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IA/0025	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/11/2013	n/a		

IB/0024	B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	07/11/2013	n/a		
IB/0022	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	14/10/2013	n/a		
IA/0020/G	This was an application for a group of variations. 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.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	20/09/2013	n/a		
IA/0019/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.II.d.2.a - Change in test procedure for the finished product - 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	16/09/2013	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	16/01/2014	SmPC, Labelling and PL	
IB/0016/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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	26/03/2013	16/01/2014	SmPC and PL	
R/0015	Renewal of the marketing authorisation.	13/12/2012	20/02/2013	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Arzerra, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
II/0012	Update of sections 4.8 and 5.1 of the SmPC with final efficacy data and updated safety data from the	21/06/2012	20/07/2012	SmPC	The final efficacy and safety results of the pivotal study Hx-CD20-406 supporting the conditional Marketing

	pivotal study Hx-CD20-406. These data had been requested as FUM 006. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Authorisation of Arzerra did not raise any concerns and confirmed the conclusions and the positive benefit/risk balance of Arzerra in the treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab.
IB/0014	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	31/05/2012	n/a		
IG/0150/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	05/04/2012	n/a		
R/0011	Renewal of the marketing authorisation.	17/11/2011	09/02/2012	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Arzerra, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.

II/0010	To update section 4.8 of the SmPC with the addition of anaphylactic shock as uncommon adverse drug reaction in the course of Arzerra administration. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/11/2011	22/12/2011	SmPC	Following two post-marketing reports of anaphylactic shock upon Arzerra administration with possible causal relationships to the medicine and two similar reports having been documented in clinical studies with Arzerra, the term anaphylactic shock was added as an Adverse Drug Reaction in the Summary of Product Characteristics (SmPC). As anaphylactic reactions are a type of infusion reactions, adequate information on the prevention and handling of such events was already included in the 'Special warnings and precautions for use' and the 'Undesirable effects' sections of the SmPC.
II/0009	To update section 4.4 of the SmPC regarding potential Hepatitis B reactivation. The MAH took the opportunity to amend a subheading in section 4.6 of the SmPC according to the QRD template as requested by the CHMP in conclusion to the assessment of PSUR 2 (PSU 009) and further amendments to the wording of this section of the SmPC were made. Finally the MAH took the opportunity to make minor changes in the Labelling. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/11/2011	22/12/2011	SmPC and Labelling	Following a post-marketing report of Hepatitis B reactivation in the course of Arzerra treament, which was not thought to be connected to the medicine, the existing warning that Hepatitis B infection can occur in the course of treatment was amended to also warn against Hepatitis B reactivation during treatment with Arzerra. This was also due to the fact that such reactivation is known to occur with other medicines with the same mechanism of action.
II/0008/G	This was an application for a group of variations. Change in the manufacturing process of the active substance, finished product and change in immediate packaging of the active substance.	23/06/2011	23/06/2011		

	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.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability				
II/0003/G	This was an application for a group of variations. Changes in the manufacture, control and container closure system of the active substance. Change in the excipients and in test procedure for the finished product. 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.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.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 B.I.b.1.f - Change in the specification parameters	16/12/2010	04/03/2011		

	and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS 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 B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs B.II.a.3.b.3 - Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological 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				
II/0004	Changes in the manufacturing process, batch size, specification parameters, test procedures, immediate packaging and pack size for the finished product. B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product	16/12/2010	21/02/2011	SmPC, Labelling and PL	

	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.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 B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral medicinal products B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
R/0005	Renewal of the marketing authorisation.	18/11/2010	21/01/2011	SmPC, Annex II, Labelling and PL	
IA/0006/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 system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance	04/01/2011	n/a		

	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.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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				
IA/0007	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	15/12/2010	n/a	SmPC, Labelling and PL	
II/0002	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	21/10/2010	08/11/2010		
II/0001/G	This was an application for a group of variations. Replacement of a manufacturer responsible for batch release. B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch	22/07/2010	29/07/2010		

	control/testing for a biol/immunol product and one of the test methods is a biol/immunol/immunochemical 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				