Humalog

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/0192	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/09/2021		PL	
WS/2115	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	02/09/2021	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).

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0190	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	21/04/2021	n/a		
IB/0188	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	31/03/2021	n/a		
IB/0189/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.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	08/03/2021	n/a		
IB/0187/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	29/01/2021	n/a		

	the manufacturing process B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				
IB/0186/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	17/12/2020	n/a		
PSUSA/1755/ 202004	Periodic Safety Update EU Single assessment - insulin lispro	26/11/2020	n/a		PRAC Recommendation - maintenance
IB/0185	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/09/2020	n/a		

WS/1909	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	04/09/2020	21/06/2021	SmPC and PL	
WS/1587/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.IV.z - Quality change - Change in Medical Devices - Other variation	23/07/2020	21/06/2021	SmPC, Annex II, Labelling and PL	The SmPC sections 1, 4.2, 4.4, 6.2, 6.4, 6.5, 6.6, 8 of the SmPC were updated in order to add a new pre-filled pen presentation. The Labelling and the PL have been updated accordingly.
IG/1267	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	06/07/2020	n/a		
WS/1700/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.1.d - Replacement or addition of a	17/04/2020	n/a		

	manufacturing site for the FP - Site which requires an initial or product specific inspection B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits				
II/0181	B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	23/01/2020	n/a		
X/0169	Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure	14/11/2019	16/01/2020	SmPC, Annex II and PL	
IB/0179	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	08/08/2019	n/a		
WS/1620	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	25/07/2019	n/a		

IB/0177	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	22/07/2019	n/a		
WS/1541	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	27/06/2019	n/a		
WS/1596	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/06/2019	n/a		
IB/0176	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	06/06/2019	n/a		
IB/0174	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g.	22/05/2019	n/a		

	duplication of line)				
IB/0171	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	19/02/2019	n/a		
WS/1537/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	24/01/2019	n/a		
IB/0170	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	04/01/2019	n/a		
IG/1025	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	06/12/2018	n/a		
IG/1007	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	16/11/2018	n/a		

	procedure				
IB/0165/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	09/10/2018	n/a		
WS/1356/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.5.b: To delete the BASAL presentations: EU/1/96/007/010, 029, 037 and 038 for Humalog Basal and EU/1/01/195/022, 023, 026 and 027 for Liprolog Basal. C.I.4: Update of sections 4.2 and 6.6 of the SmPC of Humalog/Liprolog in pre-filled pens and cartridges to address the PRAC recommendation regarding the potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia. In addition, the Worksharing applicant (WSA) took the opportunity to combine all SmPCs resulting in four SmPCs: 100 units/ml presentations, Mix 25 100 units/ml presentations, Mix50 100 units/ml presentations and 200 units/ml presentations. The	17/05/2018	21/01/2019	SmPC, Annex II, Labelling and PL	The product information has been updated to address the PRAC recommendation regarding the potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia and to add the recommendation to only use Lilly insulin cartridges in with Lilly reusable pens. In addition, the MAH has included in section 6.6 of the SmPC the recommendation that Humalog cartridges are to be used with a Lilly reusable insulin pen and should not be used with any other reusable pen as the dosing accuracy has not been established with other pens and that Liprolog cartridges are to be used with a Lilly reusable insulin pen and should not be used with any other reusable pen as the dose accuracy has not been established with other pen. The Basal presentation has also been deleted from the marketing authorisation. As a consequence of this application the labelling and package leaflet have been updated.

	MAH also brought the product information in line with the latest QRD template version 10, 02/2016, and included the recommendation to only use Lilly insulin cartridges with Lilly reusable pens. Minor editorial changes have been included. The Package Leaflet and Labelling are updated accordingly. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0164/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	12/04/2018	n/a		
WS/1314	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	01/02/2018	21/01/2019	SmPC	

PSUSA/1755/201704	Periodic Safety Update EU Single assessment - insulin lispro	30/11/2017	n/a		PRAC Recommendation - maintenance
WS/1158/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/09/2017	19/10/2017	SmPC, Annex II, Labelling and PL	
IG/0846	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	04/10/2017	n/a		
IB/0160	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	14/09/2017	19/10/2017	SmPC, Labelling and PL	
WS/1226	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	14/09/2017	n/a		

	B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products				
WS/1188	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report of a non-interventional post-authorisation safety study EUPAS 13422. This study is aimed to evaluate the impact of additional risk minimisation measures on healthcare professionals and on patients' understanding and their behaviour regarding the risk of hypoglycaemia and/or hyperglycaemia due to medication errors associated with administration of Humalog 200 U/ml KwikPen. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/09/2017	n/a		
IB/0155	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	24/03/2017	n/a		
IAIN/0156/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets,	16/03/2017	19/10/2017	SmPC, Annex II, Labelling and PL	

	ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)				
WS/1061/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.1.c (Type II): To add a new site (Eli Lilly Italia SpA, Via Gramsci, 731-733, 50019 Sesto Fiorentino, Italy) for the manufacture of Humalog and Liprolog 200U/mL, 3.0 mL cartridges. B.II.b.2.c.2 (Type IB): To add a new site (Eli Lilly Italia SpA, Via Gramsci, 731-733, 50019 Sesto Fiorentino, Italy) for the quality control testing and batch release of Humalog and Liprolog 200U/mL, 3.0 mL cartridges. The addition of the new facility results in some consequential changes to the manufacturing process in this new site: B.II.b.4 a (Type IB): to add a new 1250L batch size. B.II.b.5 b (Type IA): to add a new in-process control test method (the post filtration filter integrity test) with its test limits. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing	15/12/2016	19/10/2017	Annex II and PL	

	processes B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits				
WS/1024	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	15/12/2016	n/a		
IB/0153	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	23/11/2016	n/a		
IB/0152	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	23/11/2016	n/a		
WS/1054	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	10/11/2016	19/10/2017	SmPC, Annex II, Labelling and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0150	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	19/10/2016	n/a		
WS/0962/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	21/07/2016	n/a		
IB/0146	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	03/06/2016	n/a		
IB/0144/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.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.c - Change to in-process tests or limits applied	09/03/2016	n/a		

	during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	11/05/2016	SmPC, Labelling and PL	
WS/0879/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	28/01/2016	n/a		
WS/0844/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	28/01/2016	n/a		

	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.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
IA/0142	B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	18/12/2015	n/a		
WS/0855/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	17/12/2015	n/a		

IB/0137	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2015	11/05/2016	SmPC, Annex II and PL	
IG/0641	A.7 - Administrative change - Deletion of manufacturing sites	09/12/2015	n/a		
IA/0135	A.7 - Administrative change - Deletion of manufacturing sites	29/05/2015	11/05/2016	Annex II and PL	
IG/0567	A.7 - Administrative change - Deletion of manufacturing sites	20/05/2015	11/05/2016	Annex II and PL	
IB/0133	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	05/05/2015	n/a		
WS/0679	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.2 - Introduction of a post approval change management protocol related to the AS	26/02/2015	n/a		
IG/0515	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/12/2014	n/a		
PSUV/0128	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
IB/0129/G	This was an application for a group of variations.	30/09/2014	n/a		

	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product				
X/0125	Addition of a new strength: 200 U/ml Annex I_2.(c) Change or addition of a new strength/potency	24/07/2014	30/09/2014	SmPC, Labelling and PL	Please refer to the scientific discussion Humalog EMEA/H/C/000088/X/0125 for further information.
IG/0455	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	08/07/2014	30/09/2014	Annex II and PL	
IB/0126	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/04/2014	30/09/2014	SmPC and PL	
WS/0353/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Post-approval change management protocols to introduce changes to the manufacture of the active substance.	20/02/2014	n/a		

	B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS				
IB/0124	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/11/2013	30/09/2014	SmPC, Annex II, Labelling and PL	
IG/0363	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	16/10/2013	n/a		
IG/0362/G	This was an application for a group of variations. 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 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.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.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	11/10/2013	n/a		

IA/0121/G	This was an application for a group of variations. 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.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	11/10/2013	n/a		
N/0117	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/09/2013	30/09/2014	PL	
IB/0119/G	This was an application for a group of variations. 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 B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	05/09/2013	n/a		
IG/0337	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/08/2013	n/a		
IG/0321	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/07/2013	n/a		
IB/0116	B.II.b.5.a - Change to in-process tests or limits	16/04/2013	n/a		

	applied during the manufacture of the finished product - Tightening of in-process limits				
IB/0115	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/03/2013	n/a		
IB/0114	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	01/03/2013	n/a		
WS/0335/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This application is a grouped Type II variation: - to add an additional manufacturing site for Insulin Lispro Mix 50 cartridges. - to change the manufacturing process (equipment changes, change in batch size) - to change the in-process tests or limits applied during the manufacture of the finished product B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.3.c - Change in the manufacturing process of	13/12/2012	n/a		

	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 B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IB/0111	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	16/11/2012	n/a		
IB/0108/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	10/08/2012	25/10/2012	Annex II and PL	

	B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing				
IB/0109	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	26/06/2012	n/a		
IB/0107	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/04/2012	n/a		
IB/0106	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	13/04/2012	25/10/2012	SmPC	
WS/0196/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes to in-process tests B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on	15/03/2012	n/a		

	the overall quality of the AS B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue				
IB/0103	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	02/12/2011	n/a		
II/0099/G	This was an application for a group of variations. -To change the batch size of an intermediate. -To add a new in-process test or limit in the manufacture of the active substance. -To introduce a change in the manufacturing process of the active substance. -To change the specification parameters or limits of the active substance. -To replace a test procedure for a reagent. 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.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.2.a - Changes in the manufacturing process of	21/07/2011	21/07/2011		

	the AS - Minor change in the manufacturing process of the AS B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/07/2011	n/a	PL	
II/0100	Changes to manufacturing processes at one site to mirror those at another site doing the same manufacturing processes. 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	23/06/2011	23/06/2011		
WS/0111	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Further to a review of safety information pertaining to the risk of fluid retention and congestive heart failure with the use of insulin lispro, section 4.8 of the Summary of Product Characteristics (SmPC) is	17/03/2011	18/04/2011	SmPC and PL	Review of the safety information from Lilly Safety System and literature data sources pertaining to the risk of fluid retention (including oedema and peripheral oedema) with the use of insulin lispro suggests a causal association between insulin lispro and the adverse event of oedema. Therefore it was proposed to provide information regarding oedema in the adverse event sections of the product information. Analysis of the patients exposed to insulin lispro

	updated by adding a warning on an increased incidence of oedema. The Package Leaflet section 4 is updated accordingly. This application was submitted for a group of variations consisting of Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				between 1 January 1983 through 31 August 2010 confirmed causal association between insulin lispro and the adverse event of oedema. Consequently Summary of Product Characteristics section 4.8 is updated by adding a warning on an increased incidence of oedema. It was agreed not to mention frequency as the majority of the reports occur within the first weeks of treatment. The Package Leaflet section 4 is updated accordingly.
WS/0105	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Further to a CHMP request based on the recommendations from PhVWP, the Product Information (Summary of Product Characteristics section 4.4 and Package Leaflet section 2) is updated by adding a warning on an increased incidence of heart failure when pioglitazone is used in combination with insulin, especially in patients with predisposing factors. In addition to the above the MAH took the opportunity to update annex IIB "Other conditions" for Liprolog with the latest wording as per October 2010 CHMP announcment regarding the Pharmacovigilance system. This application was submitted for a group of	17/02/2011	24/03/2011	SmPC and PL	The PhVWP was requested to consider whether the increased risk of fluid retention and exacerbation of heart failure with the concomitant use of pioglitazone and insulin should apply to all centrally authorised insulin products. After the review of the available evidence, during its October 2010 meeting the PhVWP has concluded this review with a recommendation to the CHMP on the need to harmonise the SmPC and PL for all insulin products by including appropriate warning. The CHMP endorsed this recommendation, and in this context the Committee agreed that all centrally authorised insulin containing products should include warning on increased cardiac failure when pioglitazone is used in combination with insulin, especially in patients with predisposing factors in the in the section 4.4 of the SmPC and section 2 of the PL.

	variations consisting of Type IB variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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				
II/0097/G	This was an application for a group of variations. Change in the manufacturing process of finished product. Change to in-process test of finished product. B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	18/11/2010	06/12/2010		
IB/0098	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	27/09/2010	n/a		
II/0095	B.II.b.3b) Change in the manufacturing process of the	24/06/2010	01/07/2010		

	finished product.. Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product. B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product				
IB/0094	To increase the batch size of the finished product. B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	25/06/2010	n/a		
N/0096	The Marketing Authorisation Holder took the opportunity to update the User Manual for Humalog KwikPens. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/04/2010	n/a	PL	
II/0092	Change in the re-test period of the active substance. Update of or change(s) to the pharmaceutical documentation	18/03/2010	24/03/2010		

IB/0093	IB_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	28/01/2010	n/a		
IA/0091	To change a method of analysis to comply with Ph. Eur IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	26/11/2009	n/a		
N/0090	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/10/2009	n/a	PL	
II/0087	Change(s) to the manufacturing process for the finished product	23/07/2009	14/08/2009		
IB/0089	IB_30_b_Change in supplier of packaging components - replacement/addition	11/08/2009	n/a		
II/0083	Update of sections 4.5, 6.3 and 6.4 of the Summary of Product Characteristics and of the relevant sections of the Package Leaflet (PL). Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	01/07/2009	SmPC and PL	Further the assessment of the PSUR covering the period from 01 May 2005 to 30 April 2008, the CHMP recommended the update of the following sections of the SPC: - section 4.5 to include SSRIs (Selective Serotonin Reuptake Inhibitors) as potential hypoglycaemic antidepressants - sections 6.3 and 6.4 in order to improve the storage instructions. The package leaflet has been updated accordingly. In addition, the MAH updated the contact details of the local representative in Latvia in section 6 of the PL.

IB/0088	IB_37_a_Change in the specification of the finished product - tightening of specification limits	28/05/2009	n/a		
IB/0086	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	26/05/2009	n/a	SmPC	
IA/0085	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/05/2009	n/a		
N/0084	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/04/2009	n/a	Labelling	
IA/0082	IA_47_a_Deletion of a pharmaceutical form	08/01/2009	n/a	SmPC, Labelling and PL	
IA/0081	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	08/12/2008	n/a		
IA/0080	IA_09_Deletion of manufacturing site	19/09/2008	n/a	Annex II and PL	
IA/0078	The Marketing Authorisation Holder applied to add an alternative site for the batch release of the finished product . IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	02/09/2008	n/a	Annex II and PL	
II/0075	Change(s) to the manufacturing process of the finished product Change(s) to the manufacturing process for the	26/06/2008	22/07/2008		

	finished product				
II/0074	Change(s) to the manufacturing process of the drug substance Change(s) to the manufacturing process for the active substance	26/06/2008	22/07/2008		
IB/0077	IB_02_Change in the name of the medicinal product	06/06/2008	n/a	SmPC, Labelling and PL	
IA/0076	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	18/04/2008	n/a		
IB/0073	IB_37_b_Change in the specification of the finished product - add. of new test parameter	05/03/2008	n/a		
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/02/2008	n/a	Labelling and PL	
II/0070	Quality changes New presentation(s)	13/12/2007	31/01/2008	SmPC, Annex II, Labelling and PL	
IA/0072	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	28/01/2008	n/a		
IA/0069	IA_28_Change in any part of primary packaging material not in contact with finished product	10/08/2007	n/a		
II/0068	Update of section 4.5 of the SPC and relevant section	22/03/2007	03/05/2007	SmPC and PL	The MAH reviewed their safety database over the period 01

	of the Package Leaflet to add angiotensin II receptor blockers in the list of medicinal products that may reduce insulin requirements. Details of local representatives were updated in the PL. Update of Summary of Product Characteristics and Package Leaflet				January 1983 - 28 February 2005. No suspected interaction with an angiotensin II receptor blockers (ARB) was reported. However, the review of the safety database showed a slight increased frequency of hypoglycaemic events in patients receiving an Angiotensin Converting Enzyme (ACE) inhibitor or an ARB as concomitant medication, which supports a possible interaction with insulin. Although the overall number of reports is lower with ARBs than with ACE inhibitors, the reporting rate appears to be the same. Although the mechanism of the interaction is not well understood, both types of medicinal products share the similar endpoint to decrease the effect of angiotensin II and thus, both have the potential to increase insulin sensitivity. A published clinical study comparing the effects of an ACEI and an ARB showed more pronounced effects of the ACE inhibitors on endothelial function but similar effects on insulin sensitivity (Am J Hypertens. 2005 Feb;18(2 Pt 1):178-82) and thus support the data from the MAH safety database. Therefore section 4.5 of the SPC was updated to include ARBs in the list of medicinal products that may reduce insulin requirements.
II/0065	Change(s) to the manufacturing process for the active substance	22/02/2007	29/03/2007	Annex II	
II/0067	Update of SPC sections 4.4 and 5.1 further to the assessment of the FUM 011 to reinforce dosage instructions when using both fast-acting insulins and basal insulins for optimal glucose control, in particular nocturnal/fasting glucose control. In addition, contact details of Bulgarian and Romanian local representatives were also included.	22/02/2007	28/03/2007	SmPC and PL	The review of the results of three paediatric studies with insulin lispro showed that there were no major differences in overall safety and efficacy between insulin lispro and human regular insulin. However, in two of the studies there were differences concerning fasting and nocturnal blood glucose concentrations with higher concentrations in patients treated with insulin lispro. Therefore, and as recommended by the

	Update of Summary of Product Characteristics and Package Leaflet				CHMP, sections 4.4 and 5.1 of the SPC are revised so that all information regarding adjustment of insulin doses can be found in the same section, and to strengthen that a patient also on basal insulin must optimise dosage of both insulins to obtain glucose control across the whole day, particularly nocturnal/fasting glucose control.
IA/0066	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	08/01/2007	n/a		
II/0064	Change(s) to the manufacturing process for the finished product	16/11/2006	22/11/2006		
II/0060	Update of or change(s) to the pharmaceutical documentation	18/10/2006	14/11/2006	Annex II	
II/0062	This variation refers to an update of section 5.1 of the Summary of Product Characteristics to add clinical efficacy information based on the results of two phase IV clinical studies. Update of Summary of Product Characteristics	27/07/2006	01/09/2006	SmPC	The MAH provided the results of two randomized, open-label, crossover studies investigating the efficacy and safety of the combination of twice-daily insulin lispro LM plus metformin and once-daily insulin glargine plus metformin on overall glycaemic control, as measured by % HbA1c. Patients who participated in these studies had type 2 diabetes with inadequately controlled blood glucose, either on one or more oral anti-hyperglycaemic medications only (study IOND, N=74), or on one or more oral anti-hyperglycaemic plus one daily injection of insulin or a conventional insulin regimen consisting of once- or twice-daily NPH insulin (study IOMX, N=93). Results showed that twice-daily insulin lispro LM in combination with metformin has a greater HbA1c-lowering effect than once-daily insulin glargine with metformin, as expressed in mean % HbA1c thereafter. The new data were reflected in section 5.1 of the SPC, including those obtained

					for secondary parameters (blood glucose, frequency of hypoglycaemia, total insulin dose and bodyweight).
IA/0063	IA_28_Change in any part of primary packaging material not in contact with finished product	18/07/2006	n/a		
IB/0061	IB_20_c_Change in test procedure for an excipient - other changes	31/03/2006	n/a		
II/0059	Update of or change(s) to the pharmaceutical documentation	23/02/2006	28/02/2006		
R/0057	Renewal of the marketing authorisation.	14/12/2005	09/02/2006	SmPC, Annex II, Labelling and PL	Based on the review of the available information, the CHMP was of the opinion that the quality, the safety and the efficacy of Humalog continues to be adequately and sufficiently demonstrated and that the benefit/risk profile of Humalog continues to be favourable in the treatment of patients with diabetes mellitus.
II/0056	Change to the test procedure and/or specification of a raw material	13/10/2005	19/10/2005		
IB/0058	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	10/10/2005	n/a		
II/0054	Change(s) to the manufacturing process for the finished product	26/05/2005	17/06/2005		
IB/0055	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	07/04/2005	07/04/2005	SmPC, Annex II, Labelling and PL	

II/0053	Change(s) to the test method(s) and/or specifications for the active substance	17/02/2005	21/02/2005		
IB/0052	IB_37_a_Change in the specification of the finished product - tightening of specification limits	06/12/2004	n/a		
IA/0051	IA_05_Change in the name and/or address of a manufacturer of the finished product	22/06/2004	n/a		
II/0049	Update of or change(s) to the pharmaceutical documentation	03/06/2004	07/06/2004		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/05/2004	n/a	PL	
II/0048	Update of or change(s) to the pharmaceutical documentation	24/03/2004	30/03/2004		
N/0047	The Marketing Authorisation Holder applied for an update of the Swedish local repesentative in the package leaflet. The Marketing Authorisation Holder has also taken the opportunity to emphasize in the user manual for the prefilled pen the need to change the needle for each injection, the need to prime pen prior to to each injection and the need to confirm that the full dose of insulin has been delivered following each injection. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/02/2004	02/03/2004	PL	

I/0046	15_Minor changes in manufacture of the medicinal product	20/11/2003	24/11/2003		
II/0045	Update of Summary of Product Characteristics	24/07/2003	11/11/2003	SmPC	
I/0044	16_Change in the batch size of finished product	24/07/2003	18/09/2003		
I/0043	12_Minor change of manufacturing process of the active substance	24/07/2003	18/09/2003		
II/0042	Update of Summary of Product Characteristics and Package Leaflet	22/05/2003	07/08/2003	SmPC and PL	
I/0041	17_Change in specification of the medicinal product	04/03/2003	13/03/2003		
I/0040	30_Change in pack size for a medicinal product	13/11/2002	16/12/2002	SmPC, Labelling and PL	
I/0038	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	19/09/2002	13/11/2002	Annex II and PL	
I/0037	Introduction of a carton containing 2 vials 30_Change in pack size for a medicinal product	30/07/2002	02/10/2002	SmPC, Labelling and PL	
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/09/2002	13/11/2002	Labelling and PL	
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/05/2002	17/06/2002	Labelling and PL	

I/0035	15_Minor changes in manufacture of the medicinal product	25/04/2002	n/a		
X/0029	X-3-v_Addition of a new route of administration	15/11/2001	21/03/2002	SmPC, Annex II, Labelling and PL	
II/0034	New presentation(s)	23/08/2001	05/12/2001	SmPC, Labelling and PL	
II/0033	Update of Summary of Product Characteristics and Package Leaflet	26/07/2001	09/11/2001	SmPC and PL	
II/0032	Update of Summary of Product Characteristics	26/07/2001	09/11/2001	SmPC	
II/0031	Update of Summary of Product Characteristics	26/07/2001	09/11/2001	SmPC	
II/0030	Update of Summary of Product Characteristics and Package Leaflet	26/07/2001	09/11/2001	SmPC and PL	
II/0027	Update of or change(s) to the pharmaceutical documentation	28/06/2001	04/07/2001		
II/0025	Update of or change(s) to the pharmaceutical documentation	28/06/2001	04/07/2001		
I/0026	03_Change in the name and/or address of the marketing authorisation holder	22/02/2001	27/06/2001	SmPC, Labelling and PL	
II/0023	Update of Summary of Product Characteristics and Package Leaflet	25/01/2001	18/05/2001	SmPC, Labelling and	

				PL	
II/0028	Quality changes	26/04/2001	03/05/2001		
R/0024	Renewal of the marketing authorisation.	01/03/2001	n/a	SmPC, Annex II, Labelling and PL	
I/0022	16_Change in the batch size of finished product	28/08/2000	n/a		
I/0021	16_Change in the batch size of finished product	28/08/2000	n/a		
II/0020	Update of Summary of Product Characteristics and Package Leaflet	16/12/1999	13/04/2000	SmPC, Labelling and PL	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	20/05/1999	10/11/1999	SmPC, Labelling and PL	
II/0017	Change(s) to container	29/07/1999	n/a		
I/0019	12_Minor change of manufacturing process of the active substance	29/07/1999	n/a		
I/0018	12_Minor change of manufacturing process of the active substance	29/07/1999	n/a		
II/0016	Quality changes	24/06/1999	n/a		
I/0014	01_Change in the name of a manufacturer of the medicinal product	17/02/1999	03/06/1999	Annex II and PL	

I/0012	02_Change in the name of the medicinal product (either invented name of common name)	28/10/1998	26/01/1999	SmPC, Labelling and PL	
X/0011	X-3-iv_Change or addition of a new pharmaceutical form	23/07/1998	19/11/1998	SmPC, Labelling and PL	
II/0010	New safety warning Update of Summary of Product Characteristics and Package Leaflet	17/12/1997	11/05/1998	SmPC, Labelling and PL	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	24/09/1997	10/03/1998	SmPC, Labelling and PL	
II/0009	Update of Summary of Product Characteristics and Package Leaflet	23/07/1997	01/12/1997	SmPC, Labelling and PL	
II/0006	Update of Summary of Product Characteristics	23/07/1997	01/12/1997	SmPC	
I/0008	16_Change in the batch size of finished product	24/09/1997	n/a		
I/0003	11_Change in or addition of manufacturer(s) of active substance	13/05/1997	29/07/1997	Annex II	
II/0005	Update of Summary of Product Characteristics and Package Leaflet	18/02/1997	16/06/1997	SmPC and PL	
I/0004	12_Minor change of manufacturing process of the active substance	13/05/1997	n/a		

I/0002	01_Change following modification(s) of the manufacturing authorisation(s)	02/10/1996	05/12/1996	Annex II, Labelling and PL	
I/0001	01_Change following modification(s) of the manufacturing authorisation(s)	06/06/1996	26/08/1996	Annex II, Labelling and PL	