Toujeo

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IB/0128	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	22/11/2023		SmPC	

[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).

WS/2539	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/09/2023	n/a		
WS/2491	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/07/2023	n/a		
N/0125	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/07/2023		PL	
IB/0123	B.II.b.z - Change in manufacture of the Finished Product - Other variation	27/06/2023	n/a		
II/0121/G	This was an application for a group of variations. Please refer to the Recommendations section 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.d - Change in the batch size (including batch size ranges) of the finished product - The change	22/06/2023	n/a		Not applicable

	relates to all other pharmaceutical forms manufactured by complex manufacturing processes				
IG/1551	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	02/12/2022	n/a		
PSUSA/1751/ 202204	Periodic Safety Update EU Single assessment - insulin glargine	01/12/2022	n/a		PRAC Recommendation - maintenance
N/0118	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/11/2021	19/05/2022	PL	
II/0117/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.b - Change in the manufacturing process of	25/03/2021	n/a		

	the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product				
PSUSA/1751/202004	Periodic Safety Update EU Single assessment - insulin glargine	26/11/2020	n/a		PRAC Recommendation - maintenance
N/0116	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2020	19/05/2022	PL	
IG/1282	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/09/2020	n/a		
IAIN/0114	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/08/2020	19/05/2022	SmPC, Annex II and PL	
WS/1819/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.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.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of	05/06/2020	n/a		

	the AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
PSUSA/1751/ 201904	Periodic Safety Update EU Single assessment - insulin glargine	14/11/2019	16/01/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1751/201904.
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)	18/12/2019	n/a		
II/0108	Extension of indication to include new population for Toujeo (i.e. adolescents and children from the age of 6 years). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and risk management plan (version 6.1) are 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	17/10/2019	28/11/2019	SmPC and PL	Please refer to the Scientific Discussion (EMEA/H/C/000309/II/0108).
IB/0109	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.	13/06/2019	28/11/2019	SmPC, Labelling and	

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes			PL	
II/0105/G	This was an application for a group of variations. Please refer to the Recommendations section 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.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.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.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.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.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	31/01/2019	28/11/2019	SmPC, Annex II, Labelling and PL	With this grouping of variations the MAH has introduced a new 3 mL pre-filled pen: Toujeo "DoubleStar" with a higher insulin capacity with a total insulin content of 900 units The Toujeo "DoubleStar" pen injector and allowing delivery of multiple doses of insulin glargine in 2-unit dose increments up to a maximum single dose of 160 units. SmPC, labelling and package leaflet have been updated.

	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				
IG/0999/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	20/11/2018	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name 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/0106	Submission of the final report from a completed Phase 3b study, EFC13799: "A randomized, open-label, 2-arm, parallel-group, multicenter, 26-week study assessing the safety and efficacy of HOE901-U300 versus Lantus (insulin glargine 100 U/mL) in patients ≥ 65 years with treatment of diabetes mellitus type II (T2DM) inadequately controlled on antidiabetic regimens either including no insulin, or with basal insulin as their only insulin". The RMP (version 5) is updated to reflect the exposure data in elderly patients. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2018	n/a		N/A
PSUSA/1751/ 201804	Periodic Safety Update EU Single assessment - insulin glargine	31/10/2018	n/a		PRAC Recommendation - maintenance

PSUSA/1751/201710	Periodic Safety Update EU Single assessment - insulin glargine	17/05/2018	n/a		PRAC Recommendation - maintenance
IB/0103/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites C.I.7.b - Deletion of - a strength	21/02/2018	07/12/2018	SmPC, Annex II, Labelling and PL	
PSUSA/1751/201704	Periodic Safety Update EU Single assessment - insulin glargine	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0101/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites	13/11/2017	n/a		
II/0100	Update of sections 4.2, 4.4 and 6.6 of the SmPC in order to add a warning on the risk for medication error associated with pre-filled pens and cartridges presentations following the evaluation of a signal (EPITT 18893). The Package Leaflet is updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.	26/10/2017	07/12/2018	SmPC and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
PSUSA/1751/ 201610	Periodic Safety Update EU Single assessment - insulin glargine	05/05/2017	n/a		PRAC Recommendation - maintenance
II/0097/G	This was an application for a group of variations. B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	15/09/2016	n/a		
II/0095/G	This was an application for a group of variations. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	15/09/2016	03/10/2017	SmPC, Labelling and PL	
PSUSA/1751/ 201602	Periodic Safety Update EU Single assessment - insulin glargine	02/09/2016	n/a		PRAC Recommendation - maintenance
IG/0661	B.I.b.1.d - Change in the specification parameters	28/01/2016	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0092	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/12/2015	n/a		
IB/0093/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	04/12/2015	30/06/2016	SmPC, Annex II, Labelling and PL	
II/0091	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	26/11/2015	n/a		
IB/0090	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/09/2015	n/a		
IG/0593/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits	05/08/2015	n/a		

	applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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.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)				
IB/0088/G	This was an application for a group of variations. 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 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)	06/07/2015	n/a		
IB/0087	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	22/06/2015	30/06/2016	SmPC, Labelling and PL	

	the range of the currently approved pack sizes				
X/0079/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	26/02/2015	24/04/2015	SmPC, Annex II, Labelling and PL	Please refer to scientific summary Toujeo-H-309-X-79-G-AR
R/0086	Renewal of the marketing authorisation.	18/12/2014	17/02/2015	SmPC, 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 Optisulin continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
IB/0080	B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	03/09/2014	n/a		
IG/0475/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a	01/09/2014	n/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				
IG/0463	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	01/09/2014	n/a		
IB/0083	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)	06/08/2014	15/12/2014	SmPC and PL	
IG/0454	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	17/07/2014	n/a		
IG/0453	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	27/06/2014	n/a		
IG/0397/G	This was an application for a group of variations. B.III.2.a.1 - 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 - AS	27/01/2014	n/a		

	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits				
II/0076	Update of section 4.6 of the SmPC based on results of a meta-analysis of published data and a review of other published and post-marketing data of insulin glargine use during pregnancy. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2013	15/12/2014	SmPC and PL	Within this variation the Marketing Authorisation Holder (MAH) updated section 4.6 of the SmPC with information of the use of insulin glargine in pregnancy. In support of the application, the MAH presented results of a meta-analysis of published data on the use of insulin glargine compared to NPH in pregnancy, as well as additional available clinical data published up to 20 May 2013 and post-marketing data. The meta-analysis comprised 8 observational cohort studies with a total of 702 women with pregestational or gestational diabetes, of whom 331 received insulin glargine and 371 received NPH insulin. The meta-analysis examined maternal outcomes for efficacy and safety, and neonatal outcomes. The results of the meta-analysis did not reveal any significant increased risk associated with the use of insulin glargine compared with NPH insulin for any of the maternal or neonatal outcomes reported. With regard to the safety of insulin glargine use during pregnancy, in comparison to NPH insulin, there was no increased risk to the mother for weight gain, severe hypoglycemia, gestational/new-onset hypertension, preeclampsia, or cesarean section. While individual studies did inconsistently report differences, many of the individual findings were favourable to insulin glargine. Glycaemic control as measured by first and third trimester HbA1c was not different between the pregnant women using insulin glargine and those using NPH insulin.

					The CHMP conclusion on the meta-analysis was that it supports the overall insulin glargine program results, but could not constitute a stand-alone demonstration of glargine efficacy and safety in pregnant women with diabetes due to the limitations of the observational non-randomized design of the published reports. In addition to the meta-analysis the MAH also submitted a cumulative summary of exposure reports since the launch of the product and provided information received during the current 6-month reporting period through 21 October 2012. Pregnancy outcomes reported to date in this diabetic patient population do not suggest a new risk for patients treated with insulin glargine. This conclusion was endorsed by the CHMP.
IB/0077	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	05/12/2013	15/12/2014	SmPC, Labelling and PL	
IB/0074	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	17/09/2013	20/12/2013	SmPC, Labelling and PL	
IG/0323	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	25/07/2013	n/a		
IG/0314	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		

II/0071	Update of section 5.1 of the SmPC in order to include the results from the ORIGIN trial. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0, and some typographical errors were corrected in the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	20/12/2013	SmPC, Annex II and PL	This variation was submitted to support an update of the Lantus prescribing information based on data from the ORIGIN trial (Outcomes Reduction with an Initial Glargine INtervention). This was a multinational 7-year randomized clinical study that investigated the effect of Lantus on cardiovascular (CV) morbidity and mortality in patients with prediabetes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT]) or early Type 2 diabetes mellitus (T2DM) who had evidence of CV disease. The first coprimary endpoint (composite of the first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke) did not show any difference between insulin glargine and standard care. Also, the second coprimary endpoint (hospitalization for heart failure or revascularization procedure added to the first three components), did not show any difference. In addition, analysis by various subgroups did not reveal significant differences. Outcomes of secondary and tertiary endpoints were consistent. Therefore, it is concluded that early treatment with insulin glargine had no effect (beneficial or detrimental) on CV morbidity or cardiovascular and over-all mortality. This is an important finding that has been included in section 5.1 of the SmPC. In subjects with prediabetes, there was a numeric reduction in the percentage of subjects developing diabetes at the first post-EUF OGTT, but this effect declined after 3 months and was not clinically relevant. Cancer relationship to insulin glargine was not demonstrated in any cancer subtype (e.g. breast, colon, prostate, lung), or for new or recurrent cancers, or deaths from cancer, over 6.2 years of median follow-up. Kaplan-

					Meier curves for the first cancer diagnosed during the trial, the first new cancer diagnosed, and death due to cancer were practically superimposable between the insulin glargine and standard care groups. Although this is important information, it has not been included in the SmPC because, (i) the design of the ORIGIN study was not anticipated in order to assess the risks of cancer (ii) it is questionable whether these results could be extrapolated to long-standing diabetes with high doses of insulin (iii) available epidemiological results regarding the risk of breast cancer for longer exposures to glargine are not fully consistent across different studies. No unexpected safety issues were seen in this trial. As was expected weight did increase, and hypoglycaemia was still the major adverse event seen in association with treatment with insulin glargine. Rates of hypoglycemia in ORIGIN might be lower than those seen in other CV intervention trials in diabetes; however, as no beneficial effect of insulin glargine could be detected in this trial, an increase in the incidence of hypoglycaemia is a disadvantage. In summary, any benefit of early treatment with insulin on lower levels of HbA1 without improvement in CV outcome is outweighed by its side effects and applicability. The following text was included in section 5.1 of the SmPC to describe the design and results of this study: "The ORIGIN (Outcome Reduction with Initial Glargine INtervention) study was a multicenter, randomized, 2x2 factorial design study conducted in 12,537 participants at high cardiovascular (CV) risk with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (12% of participants) or type 2 diabetes mellitus treated with ≤1 antidiabetic oral agent (88% of participants). Participants

					were randomized (1:1) to receive insulin glargine (n=6264), titrated to reach FPG ≤95 mg/dL (5.3 mM), or standard care (n=6273). The first co primary efficacy outcome was the time to the first occurrence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, and the second co primary efficacy outcome was the time to the first occurrence of any of the first co primary events, or revascularisation procedure (coronary, carotid, or peripheral), or hospitalisation for heart failure. Secondary endpoints included all cause mortality and a composite microvascular outcome. Insulin glargine did not alter the relative risk for CV disease and CV mortality when compared to standard of care. There were no differences between insulin glargine and standard care for the two co primary outcomes; for any component endpoint comprising these outcomes; for all cause mortality; or for the composite microvascular outcome. Mean dose of insulin glargine by study end was 0.42 U/kg. At baseline, participants had a median HbA1c value of 6.4% and median on-treatment HbA1c values ranged from 5.9 to 6.4% in the insulin glargine group, and 6.2% to 6.6% in the standard care group throughout the duration of follow up. The rates of severe hypoglycaemia (affected participants per 100 participant years of exposure) were 1.05 for insulin glargine and 0.30 for standard care group and the rates of confirmed non severe hypoglycaemia were 7.71 for insulin glargine and 2.44 for standard care group. Over the course of this 6 year study, 42% of the insulin glargine group did not experience any hypoglycaemia.

					At the last on treatment visit, there was a mean increase in body weight from baseline of 1.4 kg in the insulin glargine group and a mean decrease of 0.8 kg in the standard care group.”
IG/0300	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	03/05/2013	n/a		
IG/0243	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	19/12/2012	20/12/2013	Annex II and PL	
WS/0332	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	13/12/2012	n/a		
IG/0227	A.7 - Administrative change - Deletion of manufacturing sites	13/11/2012	n/a		
IG/0192	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	06/07/2012	n/a		
II/0064	Extension of indication for the use of Optisulin in children aged 2 to less than 6 years affecting sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC. The	19/04/2012	25/05/2012	SmPC and PL	For further information please refer to the scientific conclusion: H-309-VAR-II-64-en

	Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
WS/0208	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 6.6 for SoloStar pre-filled pen presentation for the Insuman, Insuman Human Whintrop, Apidra, Lantus and Optisulin to reinforce the appropriate use of SoloStar. The Package Leaflet was proposed to be updated in accordance. Furthermore, the MAH proposed this opportunity to bring the PI in line with latest QRD template version 8.0 for Insuman, Apidra, Lantus and Optisulin. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/03/2012	20/04/2012	SmPC, Annex II, Labelling and PL	Update of the labelling documents for three sanofi-aventis insulins is proposed in this type II variation to reinforce the appropriate use of Solostar prefilled pen. This update is based on the experience gained since 2006 (e.g. following reports and questions raised by the pen users) and a continued evaluation of possible improvements of the Product Information. During this period a number of product technical complaints were received concerning the functionality of the pen, namely a blocked pen, where it is impossible to dial or inject a dose. The cause was identified that when dialling a dose and pushing the dose button without a needle attached to the pen, a mechanical pressure within the system builds, leading to a blockage of the pen mechanism. For this reason the Instructions for Use are updated to make the patient aware not to dial a dose or push the dose button without having a needle attached. There was no technical change made to the Solostar prefilled pen.
II/0066/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of	19/04/2012	19/04/2012		

	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				
II/0061	Update of sections 5.1 and 5.2 of the Summary of Products Characteristics (SmPC) to reflect new data on insulin glargine metabolites. In addition a minor change has been done to the Package Leaflet following the latest QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	24/08/2011	SmPC and PL	Insulin glargine is metabolized in the subcutaneous (SC) tissue at the carboxyl terminus of the B chain to form the two active metabolites, M1 and M2. With the availability of a new specific and quantitative bioanalytical method, pharmacokinetic (PK) samples collected in a euglycaemic clamp study were used to further explore the systemic exposure to unchanged insulin glargine and the two metabolites M1 and M2 in patients with Type 1 diabetes mellitus (T1DM) and the correlation to the established glucodynamic effect. In this clinical study insulin glargine was used as a reference at single SC doses of 0.3, 0.6, and 1.2 U/kg. The results of this study demonstrated that M1 was the principle circulating compound whereas unchanged insulin glargine and metabolite M2 were detected in only very few individual patients at few time points. The glucodynamic response correlated with metabolite M1 exposure. The CHMP agreed that this new data on insulin glargine metabolites was added to the SmPC.
IB/0063	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	28/07/2011	n/a		
IA/0062	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	01/06/2011	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0059	Changes to the cleaning procedure used for the bioreactor during 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	19/05/2011	19/05/2011		
IA/0060	A.7 - Administrative change - Deletion of manufacturing sites	07/04/2011	n/a	Annex II and PL	
II/0054	Update of product information to reflect the risk of medication errors (insulin mix-up). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	24/01/2011	SmPC and PL	The portfolio of the MAH contains several different insulins with several insulin delivery devices (IDD), including the re-usable devices (OptiPen Pro and OptiClik) and the device/drug combinations (pre-filled disposable pens OptiSet and SoloStar). The complexity regarding the various insulin treatments used in a single diabetic patient, (i.e. long acting, rapid acting; with the latter needing to be administered multiple times a day) in order to achieve optimal glycaemia control has created a situation wherein product differentiation becomes increasingly important. Adverse events associated with insulins mix-ups, often result in massive overdose of the rapid-acting insulin which may subsequently lead to hypoglycaemia, which if left untreated may be life-threatening, or result in death. In most cases, however, the patients noticed the mistake and

					took measures to avoid hypoglycaemia, which may explain the large number of cases with no AE or non-serious cases. In order to mitigate the risk of medication errors, the MAH has focused its efforts up to now on educational activities to ensure the safe administration of their insulins. The MAH has also focused on differentiation strategies for insulin products to mitigate the potential risk of administering the wrong insulin to a person with diabetes. The product information for all the insulins from this MAH has been updated through the present variation to include warnings on the risk of insulin mix-up. Additionally, the MAH will incorporate changes to the existing insulins packaging. The aim of these changes is to better differentiate the different products and to increase readability for the pharmacist, Health Care Professional or patient in order to reduce potential mix-ups.
IB/0058	Update of the Product Information (SmPC section 4.4 and Package Leaflet section 2) to add a warning on an increased incidence of cardiac failure when pioglitazone is used in combination with insulin, especially in patients with predisposing factors. 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	19/01/2011	n/a	SmPC and PL	
IA/0057	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant	20/12/2010	n/a		

	specification parameter (e.g. deletion of an obsolete parameter)				
IB/0056	Change in the Product Information (SmPC, L and PL) to include the name of the re-usable pens to be used with the cartridge presentations. B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	22/10/2010	n/a	SmPC, Labelling and PL	
IA/0055/G	This was an application for a group of variations. B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	17/09/2010	n/a		
II/0052	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	24/06/2010	07/07/2010		

R/0051	Renewal of the marketing authorisation.	18/02/2010	05/05/2010	SmPC, 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 Optisulin remains positive, but considers that its safety profile is to be closely monitored for the following reasons: - Following the publication of four epidemiological studies on the risk of (breast) cancer with the use of insulin glargine in the journal Diabetologia, concerns were raised about the safety of insulin glargine in this respect. At this moment, three post-marketing pharmacoepidemiology studies are initiated by the MAH to further investigate the possible increased risk of cancer associated with the use of insulin glargine. These studies are planned to be finished within the next three years. Based on this, and according to Article 14.3 of Regulation EC(N0) 726/2004, the CHMP is of the opinion that one additional five-year renewal on the basis of Pharmacovigilance grounds is required. - The CHMP decided that the MAH should continue to submit yearly PSURs. Therefore, based upon the safety profile of Optisulin, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0046	Update of the warning on switching between different insulins in section 4.4 of the SPC. Update of the pharmacotherapeutic group in section 5.1 of the SPC to comply with the latest QRD template. Section	24/09/2009	04/11/2009	SmPC and PL	Section 4.4 of the SPC was updated in order to harmonize the information between all Sanofi-Aventis Deutschland GmbH insulins regarding the transfer from one insulin to another. The information given to the prescriber has been

	6 of the Package Leaflet is also updated with an additional telephone number for Italy. Update of Summary of Product Characteristics and Package Leaflet				made clearer. Section 5.1 of the SPC was updated to comply with the latest version of the QRD template for the SPC. Only the lowest available level of this pharmacotherapeutic group is now provided. Finally, Section 6 of Package Leaflet was also updated with an additional telephone number for Italy.
IB/0050	IB_30_b_Change in supplier of packaging components - replacement/addition	28/09/2009	n/a		
IB/0049	IB_30_b_Change in supplier of packaging components - replacement/addition	28/09/2009	n/a		
II/0044	Update of Summary of Product Characteristics and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	17/09/2009	SmPC and PL	Update to section 6.6 of the SPC to clarify the instructions for use of the pre-filled pen Optiset and the pre-filled pen Solostar. The package leaflet was updated accordingly. The contact details of the local representative in Poland were also updated in the PL. Minor linguistic changes introduced in the SPC.
IB/0047	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	11/09/2009	n/a		
IA/0048	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	04/09/2009	n/a	Annex II and PL	
II/0045	Changes in the batch size of the manufacturing process of the finished product for the 10 ml vials presentation	23/07/2009	30/07/2009		

	Change(s) to the manufacturing process for the finished product				
II/0043	Addition of presentations containing a new pen delivery system. New presentation(s)	22/01/2009	09/03/2009	SmPC, Labelling and PL	
II/0042	Registration of a cartridge system to be used with an insulin pen delivery device. New presentation(s)	22/01/2009	09/03/2009	SmPC, Labelling and PL	
II/0041	Addition of presentations containing a new pen delivery system. New presentation(s)	22/01/2009	09/03/2009	SmPC, Labelling and PL	
II/0039	To include an additional site for manufacture and batch release 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	23/10/2008	28/11/2008	Annex II	
II/0040	Change in the holding time of a manufacturing intermediate for the manufacturing process of insulin glargine solution for injection 100 Units/ml in 3 ml cartridges. Change(s) to the manufacturing process for the	20/11/2008	27/11/2008		

	finished product				
II/0038	To update section 5.1 of the SPC with additional information on the effects of Optisulin (insulin glargine) on progression of diabetic retinopathy, based on results of study HOE901/4016. Update of Summary of Product Characteristics	24/07/2008	17/09/2008	SmPC	This variation concerns the update of section 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics for Optisulin to include the results of study HOE901/4016, an open-label 5-year NPH-controlled study (NPH given bid) in 1024 type 2 diabetic patients in which progression of retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy (ETDRS) scale was investigated by fundus photography. The results demonstrated that for all eye disease variables based on blinded evaluation of fundus photographs, there were no differences between treatments for 5 years with Optisulin versus NPH insulin as basal insulin.
II/0034	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	25/06/2008	SmPC, Labelling and PL	Update of the Product Information (PI) to harmonise the Summary of Product Characteristics (SPC), Labelling and Package Leaflet of the sanofi-aventis insulin containing products (insuline glargine, insulin glulisine and insulin human). Particularly for Lantus, the SPC has been revised and the package leaflet has been updated to reflect the outcome of the Readability User Testing performed to demonstrate the readability and usefulness of the PL to patients.
II/0033	Update of section 4.2 of the Summary of Product Characteristics and section 3 of the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	31/03/2008	SmPC and PL	The SPC of Optisulin has been updated to reflect the flexible timing in the administration of the doses of insulin glargine. In the flexible dosing the product can be administered any time during the day as long as it is the same time each day, compared to morning or evening administration previously authorised. The Package Leaflet has been updated accordingly.

II/0032	Update of the 4.8 of the Summary of Product Characteristics and Package Leaflet to include information on the safety in children. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	31/03/2008	SmPC and PL	Following the assessment of a clinical trial and post-marketing surveillance data in the paediatric population, the CHMP requested that section 4.8 of the SPC should be updated to reflect safety information on patients ?18 years. The changes were supported by the study HOE901/4030 which was an open label, randomised, gender-stratified, and parallel-group. Section 4.8 of the SPC has been updated with the following wording: "In general, the safety profile for patients ? 18 years of age is similar to the safety profile for patients > 18 years. The adverse event reports received from Post Marketing Surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in patients ? 18 years of age than in patients > 18 years. No clinical study safety data are available in patients below 6 years of age." The PL has been updated accordingly.
II/0031	Update of Summary of Product Characteristics section 4.1 to include the indication for children of 6 years of age or above. The Package Leaflet has been amended accordingly. Extension of Indication	21/02/2008	31/03/2008	SmPC and PL	Please refer to the scientific discussion: Optisulin H-309-II-31-AR
IB/0037	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	01/02/2008	n/a		
IB/0036	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	01/02/2008	n/a		

II/0026	Change(s) to the manufacturing process for the active substance	24/01/2008	30/01/2008		
IA/0035	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	09/01/2008	n/a		
II/0028	Quality changes of the drug product. Quality changes	13/12/2007	19/12/2007		
IB/0030	IB_27_b_Change to test proc. of immediate packaging - other changes (incl. replacement/addition)	17/12/2007	n/a		
II/0027	Update of section 4.4 of the SPC to include a cross-reference to a warning on antibody formation already present in the section 4.8. The Package Leaflet was amended to update the list of local representatives in section 6 and to include some minor editorial corrections. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	14/11/2007	SmPC and PL	The MAH has updated section 4.4 'Special Warnings and precautions for use' of the SPC to include a cross-reference to antibody formation already present in section 4.8 'Undesirable effects', as previously requested by the CHMP. The Package Leaflet was amended to update the list of local representatives and to include some minor editorial corrections.
IB/0029	Addition of an alternative test procedure of the finished product used for release and stability testing IB_38_c_Change in test procedure of finished product - other changes	31/10/2007	n/a		
IA/0025	IA_38_a_Change in test procedure of finished	20/06/2007	n/a		

	product - minor change to approved test procedure				
IA/0024	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	13/04/2007	n/a		
IB/0023	IB_38_c_Change in test procedure of finished product - other changes	16/03/2007	n/a		
IA/0022	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	08/02/2007	n/a		
IB/0021	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	21/08/2006	n/a		
II/0020	This variation relates to an update of section 4.6 "Pregnancy and Lactation" of the Summary of Product Characteristics, following CHMP request further to the assessment of the FUM 025.1. The product information has also changed according to the latest version of the QRD templates. Update of Summary of Product Characteristics	28/06/2006	07/08/2006	SmPC	Further to their conclusions of the assessment of cumulatively reported data of exposure during pregnancy, the CHMP requested a variation to change the section 4.6 of the SPC "Pregnancy and Lactation" to reflect the latest available information on exposed pregnancies. The product information has also changed according to the latest version of the QRD templates.
II/0018	Change(s) to the manufacturing process for the finished product	23/03/2006	30/03/2006		
IA/0019	IA_01_Change in the name and/or address of the marketing authorisation holder IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	03/03/2006	n/a	SmPC, Annex II, Labelling and PL	

	IA_05_Change in the name and/or address of a manufacturer of the finished product				
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/09/2005	n/a	PL	
R/0016	Renewal of the marketing authorisation.	21/04/2005	08/07/2005	SmPC, Annex II, Labelling and PL	
II/0014	Change(s) to the test method(s) and/or specifications for the active substance Change in formulation	16/03/2005	27/04/2005	SmPC, Labelling and PL	
II/0015	Change(s) to the test method(s) and/or specifications for the active substance	17/02/2005	25/02/2005		
II/0013	The Marketing Authorisation Holder applied for the use of an alternative rubber stopper for the 3 ml cartridge and for an extension of the shelf life of the finished product as packaged for sale, from 2 years to 3 years, for the current and proposed alternative container closure system of the 3 ml cartridge presentations. Change(s) to container	18/11/2004	10/01/2005	SmPC	
II/0012	The Marketing Authorisation Holder applied for the addition of a new manufacturing facility for the active substance, a site where this active substance is currently manufactured.	16/09/2004	30/09/2004		

	Change(s) to the manufacturing process for the active substance				
II/0011	Update of section 6.6 of the Summary of Product Characteristics to include instructions and warnings for handling the OptiPen in case of mechanical defects further to a CHMP request. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/06/2004	31/08/2004	SmPC, Labelling and PL	Following reports received from patients who had experienced difficulties with insulin administration by OptiPen the CHMP concluded at the March 2004 plenary meeting that the Product Information for Optisulin solution for injection in a cartridge should be amended to include a warning in the Product Information describing that Optipen should not be used in case of mechanical defects. Some devices were investigated after the reported failure and the manufacturer's reports conclude in a suspected user's failure rather than a device failure. Some of the patients experienced serious clinical events and there have been a relatively high number of these user errors: several patients indicated that they were not aware whether the pen had actually delivered a dose or not and some mentioned that the displayed dose did not seem to correspond to what was actually set or seem to be delivered. It was remarked that the Optipen has an electronic display indicating the dose setting. This could be a potential source for malfunctioning since it may be hampered by electromagnetic field influences (microwave, TV). The pens returned and investigated appeared to function well. However, the current SPC and PL of Optisulin solution for injection in a cartridge do not provide instructions for handling the OptiPen in case of mechanical defects. Information was therefore added to section 6.6 of the SPC. This information was also added to the labelling of the outer packaging as well as clarification that the cartridges

					are to be used in conjunction with OptiPen only. To section 3 of the Package Leaflet was added the advice to follow the manufacturer's instructions for using the pen carefully for loading the cartridge, attaching the needle, and administering the insulin injection, to see instructions for using the pen and not to use OptiPen if it is damaged.
II/0010	Update to include information regarding the effect of atypical antipsychotic products and protease inhibitors on hyperglycaemia in section 4.5 of the Summary of Product Characteristics (SPC). Section 2 of the Package Leaflet has been updated accordingly. In addition the MAH applied to amend section 4.6 of the SPC to bring it in line with the wording in section 4.6 of the Optisulin SPC (EU/1/00/133/001-008). Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	13/07/2004	SmPC, Annex II and PL	Based on publications submitted in this variation, it may be concluded that patients receiving atypical antipsychotics medicinal products or protease inhibitors are at risk of hyperglycemia, whether or not they have pre-existing diabetes. This conclusion supports an update of section 4.5 of the SmPC and a consistent update is made to the package leaflet .The CHMP concluded that protease inhibitors and atypical antipsychotic medicinal product (e.g. clozapine and olanzapine) should be added to the list of substances, which may reduce the blood-glucose lowering effect listed in section 4.5 of the SPC.
II/0009	The Marketing Authorisation Holder applied for the following changes in the manufacturing process of the active substance: the use of recombinant non animal trypsin as an alternate source to the porcine source at step 9 (tryptic cleavage), the implementation of a citrate washing procedure in step 13 (second crystallisation and drying) instead of the current washing procedure, the removal of the option of using side-fraction for re-chromatography at step 12 and deletion of associated testing of the side-fraction.	22/04/2004	26/04/2004		

	Change(s) to the manufacturing process for the active substance				
II/0008	Update of section 4.4 of the Summary of Product Characteristics (SPC) and section 4 of the Package Leaflet to include a warning concerning hypoglycaemia as requested by the CHMP and to include a class wording regarding hypoglycaemic reactions after transfer from animal source insulin to human insulins. Update of Summary of Product Characteristics and Package Leaflet	17/12/2003	02/03/2004	SmPC and PL	The CHMP requested an update of section 4.4 of the SC to include a class labelling for all centrally authorised human insulins (conclusions September 2001 CHMP) relating to hypoglycaemic reactions after transfer from animal source insulin to human insulin. This information was added to section 4.4. of the SPC and section 4 of the Package Leaflet. Following the assessment of the 3rd PSUR the MAH was requested to add SPC a warning that due to the prolonged effect of subcutaneous insulin glargine the recovery from hypoglycaemia may be delayed. The MAH was requested by CPMP to include this wording in section 4.4 of the SPC after the text "Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patients awareness of hypoglycaemia". Further changes in sections 4.6, 4.8, 5.1, 5.3, 6.4, 6.5 and 8 of the SPC were made to bring the SPC in line with the QRD templates and to update the ATC code. Changes regarding QRD templates and an update of the local representatives have also been proposed for the Package Leaflet (introduction section, sections 2, 3, 4, 5, 6).
II/0006	The Marketing Authorisation Holder applied for minor changes to 3 steps of the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	25/09/2003	30/09/2003		

I/0007	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	19/06/2003	25/06/2003		
I/0005	16_Change in the batch size of finished product	25/04/2003	02/05/2003		1 Introduction The company has applied for an increase in the batch size of the bulk solution of the finished product (3 ml cartridges) from 200 - 400 liter (initially approved) up to 1600 liter. For the 10 ml filling this increase in batch size has already been submitted and approved (EMEA/H/C/309/II/04). In support of the variation the company has submitted validation data, a quality expert statement and an updated process narrative/flow chart. 2 Chemical, pharmaceutical and biological aspects The bulk solution of 1600 l is distributed into movable vessels of 400 l capacity each. As a result the filling process itself remains unaffected. The effect on the filling duration is appropriately validated with media fills. The (in-process and final product quality control) results of three batches were within established limits and met all specifications approved in the MAA. A comparison with three batches prepared on the 400 ml scale indicate no differences between batches produced on the 400 ml scale and the 1600 l scale. Therefore, the proposed variation to increase the batch size for the 3 ml cartridges from 400 l into 1600 l can be approved. This variation also fulfills follow-up measure 011.

II/0004	Addition of a pack size: vial with 10 ml contents New presentation(s)	25/04/2002	09/08/2002	SmPC, Labelling and PL	
II/0003	Change in the insulin glargine production process. Change(s) to the manufacturing process for the active substance	27/06/2001	02/08/2001		
II/0002	Change(s) to the manufacturing process for the active substance	27/06/2001	02/08/2001		
II/0001	Demonstration of TSE compliance. Update of or change(s) to the pharmaceutical documentation	26/04/2001	02/08/2001		