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REQUEST FOR FILING A CONTINUATION OR DIVISION OF AN INTERNATIONAL APPLICATION

Docket Number	ANTICIPATION CLASSIFICATION OF THIS APPLICATION		PRIOR APPLICATION EXAMINER	ART UNIT
6683.204-US	Class	Subclass		

Address to: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

113007 U.S.PTO
11/435977

051706

This is a request for filing a [X] continuation [ ] divisional application under 37 CFR 1.53(b) of pending prior international application Number PCT DK2004/000792, filed on November 18, 2004

entitled **PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES**, which designated the United States.

(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE ($)	(5) TOTALS ($)
TOTAL CLAIMS (37 CFR 1.16(i))	44 - 20 =	24	x 50 =	1200.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 - 3 =	2	x 200 =	400.00
APPLICATION SIZE FEE (37 CFR 1.16(s)) If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
MULTIPLE DEPENDENT CLAIMS (37 CFR 1.16(j))			N/A	
			BASIC FEE (37 CFR 1.16(a))	300.00
			SEARCH FEE (37 CFR 1.16(k))	500.00
			EXAMINATION FEE (37 CFR 1.16(o))	200.00
			Total of above	2600.00
Reduction by 50% for filing small entity (Note 37 CFR 1.27)				
			Total	2600.00

1. [X] Enclosed are the specification, claims and drawing(s).

2. [ ] Applicant claims small entity status. See 37 CFR 1.27.

3. [X] The Director is hereby authorized to charge any fees which may be required under 37 CFR 1.16 and 1.17, or credit any overpayment of Deposit Account No. 14-1447. A duplicate copy of this sheet is enclosed.

4. [ ] A check in the amount of $ _____ is enclosed.

5. [ ] Payment by credit card. Form PTO-2038 is attached.

6. [X] Application Data Sheet is enclosed. See 37 CFR 1.76.

7. [X] If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:

[X] Continuation [ ] Divisional of prior PCT application No.: DK2004/000792, filed on November 18, 2004

PTO/SB/13/PCT (01-05)
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REQUEST FOR FILING A CONTINUING APPLICATION OF AN INTERNATIONAL APPLICATION

8. [X] A declaration under CFR 1.63 is enclosed. (unsigned)

9. [X] Priority of foreign application number PA 2003 01719, filed on November 20, 2003, in Denmark is claimed under 35 U.S.C. 119(a)-(d).
Priority of US application number60/524,653, filed on November 24, 2003, in the US is claimed under 35 U.S.C. 119(e)

10. [ ] A preliminary amendment is enclosed.

11. [ ] Also enclosed: _____

Address all future correspondence to: (May only be completed and signed by applicant, or attorney or agent of record).

23650

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Richard W. Bork — **May 17, 2006**
Signature — Date

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[ ] Inventor(s)/Applicant(s)

[ ] Assignee of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

[ ] Attorney or agent of record

[X] Filed under 37 CFR 1.34
Registration number if acting under 37 CFR 1.34 36,459

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 2 forms are submitted.

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
EXPRESS MAIL CERTIFICATE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application for
Title: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES
Applicants: Pedersen et al.

Sir:

Express Mail Label No. EV 732210367 US

Date of Deposit: May 17, 2006

I hereby certify that the following attached paper(s) or fee

1. Request for Filing a Continuation or Division of an International Application (in duplicate)
2. Patent Application (34 pages of specification, 1 page of abstract, 7 sheets of drawings)
3. Unexecuted Combined Declaration and Power of Attorney
4. Application Data Sheet (4 pages)
5. Sequence Listing Transmittal Letter
6. Sequence Listing (1 page)
7. Computer Readable Format (CRF) of Sequence Listing

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, PO Box 1450, Alexandria VA 22313-1450.

Rashida Haji
(Name of person mailing paper(s) or fee)

Rashida Haji
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Mailing Address:
Novo Nordisk Inc.
Customer Number 23650

Use the following customer number for all correspondence regarding this application.

23650
PATENT TRADEMARK OFFICE

PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

CROSS REFERENCE TO RELATED APPLICATIONS

This Application is a continuation of International Application serial no. PCT/DK2004/000792 filed November 18, 2004 and claims priority from U.S. Application serial no. 60/524653 filed November 24, 2003 and from Danish Application serial no. PA 2003 01719 filed November 20, 2003.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations comprising a peptide and propylene glycol, to methods of preparing such formulations, and to uses of such formulations in the treatment of diseases and conditions for which use of the peptide contained in such formulations is indicated. The present invention further relates to methods for reducing the clogging of injection devices by a peptide formulation and for reducing deposits on production equipment during production of a peptide formulation.

BACKGROUND OF THE INVENTION

The inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known and one of the more common isotonic agents used in such formulations is mannitol. However, the present inventors have observed that mannitol causes problems during the production of peptide formulations as it crystallizes resulting in deposits in the production equipment and in the final product. Such deposits increase the need to clean the filling equipment during production of the formulation and this results in reduced production capability. In addition, such deposits may also result in reduced yield of the final product since vials/cartridges containing the peptide formulation may need to be discarded if particles are present. Finally, the present inventors have observed that in peptide formulations to be administered by injection, the presence of mannitol results in clogging of injection devices.

Accordingly, it is desirable to identify an alternative isotonic agent to mannitol for inclusion in peptide-containing formulations and in particular, for inclusion in peptide formulations which are administered by injection.

SUMMARY OF THE INVENTION

The present inventors have discovered that peptide formulations containing propylene glycol at certain concentrations exhibit reduced deposits in production equipment and in the final product and also exhibit reduced clogging of injection devices. The present composi-

tions may be formulated with any peptide and are also physically and chemically stable thus rendering them shelf-stable and suitable for invasive (eg. injection, subcutaneous injection, intramuscular, intraveneous or infusion) as well as non-invasive (eg nasal, oral, pulmonary, transdermal or transmucosal e.g. buccal) means of administration.

The present invention therefore relates to a pharmaceutical formulation comprising a peptide and propylene glycol, where the propylene glycol is present in a concentration of 1-100 mg/ml and the pH of the formulation is from 7-10. In a preferred embodiment, the pharmaceutical formulations of the invention further contain a buffer and a preservative.

The present invention also relates to methods for producing the pharmaceutical formulations of the invention.

In one embodiment, the method for preparing a peptide formulation comprises:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;

b) preparing a second solution by dissolving the peptide in water;

c) mixing the first and second solutions; and

d) adjusting the pH of the mixture in c) to the desired pH.

In another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a first solution by dissolving preservative and buffer in water;

b) adding propylene glycol to the first solution;

c) mixing the first solution with a second solution containing peptide dissolved in water; and

d) adjusting the pH of the mixture in c) to the desired pH.

In yet another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a solution by dissolving preservative, buffer and propylene glycol in water;

b) adding the peptide to the solution of step a); and

c) adjusting the pH of the solution of step b) to the desired pH.

The present invention further relates to methods of treatment using the pharmaceutical formulations of the invention where the compositions are administered in an amount effective to combat the disease, condition, or disorder for which administration of the peptide contained in the formulation is indicated.

In addition the present invention also relates to a method for reducing deposits on production equipment during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

The present invention also relates to a method for reducing deposits in the final product during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

The present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a photograph of dried droplets on microscope slides of from left to right, placebo (no peptide) formulations containing no isotonic agent (e only water, preservative and buffer), mannitol, sorbitol, xylitol, sucrose or glycerol as the isotonic agent with the far right slide containing mannitol with peptide Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

Figure 2 shows light microscopy pictures of from left to right, some of the dried droplets of placebo formulations containing mannitol, arginin, inositol or glycerol as the isotonic agent.

Figure 3 shows light microscopy pictures of clogged needles dosed with placebo formulations containing myoinositol, maltose or glycerol as the isotonic agent.

Figure 4 shows light microscopy pictures of deposits on needles dosed with placebo formulations containing glycine, lactose or mannitol as the isotonic agent.

Figure 5 shows filling equipment after 24 hours simulated filling with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) medium containing myo-inositol.

Figure 6 shows deposits on filling equipment after 24 hours simulated filling with a mannitol-containing placebo formulation.

Figure 7 shows deposits on needles dosed with mannitol (top panel) and propylene glycol (bottom panel)-containing Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) formulations.

DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical formulation comprising a peptide or a mixture of peptides and propylene glycol where the final concentration of propylene glycol in the formulation is 1-100 mg/ml and the pH of the formulation is in the range of from 7-10.

The pharmaceutical formulations of the invention are found to be optimal for production because they exhibit reduced deposits in production equipment relative to formulations containing other isotonicity agents as measured by the simulated filling studies described in the Examples. In addition, the pharmaceutical formulations of the invention are found to be optimal for use in injection devices because they exhibit reduced clogging of the injection devices relative to formulations containing other isotonicity agents as measured by the simulated in use studies described in the Examples.

The formulations of the present invention may be formulated with any peptide where examples of such peptides include, but are not limited to, glucagon, human growth hormone (hGH), insulin, aprotinin, FactorVII, tissue plasminogen activator (TPA), FactorVIIa, FFR-FactorVIIa, heparinase, ACTH, Heparin Binding Protein, corticotropin-releasing factor, angiotensin, calcitonin, glucagon-like peptide-1, glucagon-like peptide-2, insulin-like growth factor-1, insulin-like growth factor-2, fibroblast growth factors, gastric inhibitory peptide, growth hormone-

releasing factor, pituitary adenylate cyclase activating peptide, secretin, enterogastrin, somatostatin, somatomedin, parathyroid hormone, thrombopoietin, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, oxytocin, opiods, DPP IV, interleukins, immunoglobulins, complement inhibitors, serine protease inhibitors, cytokines, cytokine receptors, PDGF, tumor necrosis factors, tumor necrosis factors receptors, growth factors and analogues as well as derivatives thereof where each of these peptides constitutes an alternative embodiment of the present invention.

In the present application, the designation "an analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either at the N-terminal end or at the C-terminal end of the parent peptide or both. Typically " an analogue" is a peptide wherein 6 or less amino acids have been substituted and/or added and/or deleted from the parent peptide, more preferably a peptide wherein 3 or less amino acids have been substituted and/or added and/or deleted from the parent peptide, and most preferably, a peptide wherein one amino acid has been substituted and/or added and/or deleted from the parent peptide.

In the present application, "a derivative" is used to designate a peptide or analogue thereof which is chemically modified by introducing an organic substituent e.g. ester, alkyl or lipophilic functionalities, on one or more amino acid residues of the peptide or analogue thereof.

In one embodiment, the peptide to be included in the formulation of the invention is a GLP-1 agonist where "a GLP-1 agonist" is understood to refer to any peptide which fully or partially activates the human GLP-1 receptor. In a preferred embodiment, the "GLP-1 agonist" is any peptide that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 μM, e.g. below 100 nM as measured by methods known in the art (see e.g. WO 98/08871) and exhibits insulinotropic activity, where insulinotropic activity may be measured in vivo or in vitro assays known to those of ordinary skill in the art. For example, the GLP-1 agonist may be administered to an animal and the insulin concentration measured over time.

Methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S) and examples of suitable GLP-1 analogues and derivatives which can be used according to the present invention includes those referred to in WO 99/43705 (Novo Nordisk A/S), WO 99/43706 (Novo Nordisk A/S), WO 99/43707 (Novo Nordisk A/S), WO 98/08871 (analogues with lipophilic substituent) and in WO 02/46227 (analogues fused to serum albumin or to Fc portion of an Ig).(Novo Nordisk A/S), WO 99/43708 (Novo Nordisk A/S), WO

99/43341 (Novo Nordisk A/S), WO 87/06941 (The General Hospital Corporation), WO 90/11296 (The General Hospital Corporation), WO 91/11457 (Buckley et al.), WO 98/43658 (Eli Lilly & Co.), EP 0708179-A2 (Eli Lilly & Co.), EP 0699686-A2 (Eli Lilly & Co.), WO 01/98331 (Eli Lilly & Co).

In one embodiment, the GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

In one embodiment, the GLP-1 agonist is a derivative of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, which comprises a lipophilic substituent.

In this embodiment of the invention, the GLP-1 derivative preferably has three lipophilic substituents, more preferably two lipophilic substituents, and most preferably one lipophilic substituent attached to the parent peptide (ie GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue), where each lipophilic substituent(s) preferably has 4-40 carbon atoms, more preferably 8-30 carbon atoms, even more preferably 8-25 carbon atoms, even more preferably 12-25 carbon atoms, and most preferably 14-18 carbon atoms.

In one embodiment, the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

In another embodiment, the lipophilic substituent is a straight-chain or branched alkyl group.

In yet another embodiment, the lipophilic substituent is an acyl group of a straight-chain or branched fatty acid. Preferably, the lipophilic substituent is an acyl group having the formula $CH_3(CH_2)_nCO$-, wherein n is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-. In a more preferred embodiment, the lipophilic substituent is tetradecanoyl. In a most preferred embodiment, the lipophilic substituent is hexadecanoyl.

In a further embodiment of the present invention, the lipophilic substituent has a group which is negatively charged such as a carboxylic acid group. For example, the lipophilic substituent may be an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid of the formula $HOOC(CH_2)_mCO$-, wherein m is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- or $HOOC(CH_2)_{22}CO$-.

In the GLP-1 derivatives of the invention, the lipophilic substituent(s) contain a functional group which can be attached to one of the following functional groups of an amino acid of the parent GLP-1 peptide:

(a) the amino group attached to the alpha-carbon of the N-terminal amino acid,

(b) the carboxy group attached to the alpha-carbon of the C-terminal amino acid,

(c) the epsilon-amino group of any Lys residue,

(d) the carboxy group of the R group of any Asp and Glu residue,

(e) the hydroxy group of the R group of any Tyr, Ser and Thr residue,

(f) the amino group of the R group of any Trp, Asn, Gln, Arg, and His residue, or

(g) the thiol group of the R group of any Cys residue.

In one embodiment, a lipophilic substituent is attached to the carboxy group of the R group of any Asp and Glu residue.

In another embodiment, a lipophilic substituent is attached to the carboxy group attached to the alpha-carbon of the C-terminal amino acid.

In a most preferred embodiment, a lipophilic substituent is attached to the epsilon-amino group of any Lys residue.

In a preferred embodiment of the invention, the lipophilic substituent is attached to the parent GLP-1 peptide by means of a spacer. A spacer must contain at least two functional groups, one to attach to a functional group of the lipophilic substituent and the other to a functional group of the parent GLP-1 peptide.

In one embodiment, the spacer is an amino acid residue except Cys or Met, or a dipeptide such as Gly-Lys. For purposes of the present invention, the phrase "a dipeptide such as Gly-Lys" means any combination of two amino acids except Cys or Met, preferably a dipeptide wherein the C-terminal amino acid residue is Lys, His or Trp, preferably Lys, and the N-terminal amino acid residue is Ala, Arg, Asp, Asn, Gly, Glu, Gln, Ile, Leu, Val, Phe, Pro, Ser, Tyr, Thr, Lys, His and Trp. Preferably, an amino group of the parent peptide forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

Preferred spacers are lysyl, glutamyl, asparagyl, glycyl, beta-alanyl and gamma-aminobutanoyl, each of which constitutes an individual embodiment. Most preferred spacers are glutamyl and beta-alanyl. When the spacer is Lys, Glu or Asp, the carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ε-amino group of Lys and the lipophilic substituent. In one embodiment, such a further spacer is succinic acid which forms an amide bond with the ε-amino group of Lys and with an amino group present in the lipophilic substituent. In another embodiment such a further spacer is Glu or Asp which forms an amide bond with the ε-amino group of Lys and another amide bond with a carboxyl

group present in the lipophilic substituent, that is, the lipophilic substituent is a N^{ε}-acylated lysine residue.

In another embodiment, the spacer is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, which spacer forms a bridge between an amino group of the parent peptide and an amino group of the lipophilic substituent. Preferably, the spacer is succinic acid.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_pNH\text{-}CO(CH_2)_qCO\text{-}$, wherein p is an integer from 8 to 33, preferably from 12 to 28 and q is an integer from 1 to 6, preferably 2.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_rCO\text{-}NHCH(COOH)(CH_2)_2CO\text{-}$, wherein r is an integer from 4 to 24, preferably from 10 to 24.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_sCO\text{-}NHCH((CH_2)_2COOH)CO\text{-}$, wherein s is an integer from 4 to 24, preferably from 10 to 24.

In a further embodiment, the lipophilic substituent is a group of the formula $COOH(CH_2)_tCO\text{-}$ wherein t is an integer from 6 to 24.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_uCH_3$, wherein u is an integer from 8 to 18.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_vCO\text{-}NH\text{-}(CH_2)_z\text{-}CO$, wherein v is an integer from 4 to 24 and z is an integer from 1 to 6.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}COCH((CH_2)_2COOH)NH\text{-}CO(CH_2)_wCH_3$, wherein w is an integer from 10 to 16.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_2CH(COOH)NHCO(CH_2)_xCH_3$, wherein x is zero or an integer from 1 to 22, preferably 10 to 16.

In yet another embodiment the GLP-1 agonist is Arg^{34}, $Lys^{26}(N^{\varepsilon}\text{-}(\gamma\text{-}Glu(N^{\alpha}\text{-}$hexadecanoyl$)))$-GLP-1(7-37).

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Gly^8-GLP-1(7-36)-amide, Gly^8-GLP-1(7-37), Val^8-GLP-1(7-36)-amide, Val^8-GLP-1(7-37), Val^8Asp^{22}-GLP-1(7-36)-amide, Val^8Asp^{22}-GLP-1(7-37) , Val^8Glu^{22}-GLP-1(7-36)-amide , Val^8Glu^{22}-GLP-1(7-37), Val^8Lys^{22}-GLP-1(7-36)-amide, Val^8Lys^{22}-GLP-1(7-37), Val^8Arg^{22}-GLP-1(7-36)-amide, Val^8Arg^{22}-GLP-1(7-37), Val^8His^{22}-GLP-1(7-36)-amide, Val^8His^{22}-GLP-1(7-37), analogues thereof and derivatives of any of these.

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Arg^{26}-GLP-1(7-37); Arg^{34}-GLP-1(7-37); Lys^{36}-GLP-1(7-37); $Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Arg^{26,34}$-GLP-1(7-37); $Arg^{26,34}Lys^{40}$-GLP-1(7-37); $Arg^{26}Lys^{36}$-GLP-1(7-37); $Arg^{34}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{22}$-GLP-1(7-37); $Met^{8}Arg^{22}$-GLP-1(7-37);$Gly^{8}His^{22}$-GLP-1(7-37); $Val^{8}His^{22}$-GLP-1(7-37); $Met^{8}His^{22}$-GLP-1(7-37);His^{37}-GLP-1(7-37); Gly^{8}-GLP-1(7-37); Val^{8}-GLP-1(7-37); Met^{8}-GLP-1(7-37);$Gly^{8}Asp^{22}$-GLP-1(7-37); $Val^{8}Asp^{22}$-GLP-1(7-37); $Met^{8}Asp^{22}$-GLP-1(7-37);$Gly^{8}Glu^{22}$-GLP-1(7-37); $Val^{8}Glu^{22}$-GLP-1(7-37); $Met^{8}Glu^{22}$-GLP-1(7-37); $Gly^{8}Lys^{22}$-GLP-1(7-37); $Val^{8}Lys^{22}$-GLP-1(7-37); $Met^{8}Lys^{22}$-GLP-1(7-37); $Gly^{8}Arg^{22}$-GLP-1(7-37); $Val^{8}Lys^{22}His^{37}$-GLP-1(7-37); $Gly^{8}Glu^{22}His^{37}$-GLP-1(7-37); $Val^{8}Glu^{22}His^{37}$-GLP-1(7-37); $Met^{8}Glu^{22}His^{37}$-GLP-1(7-37);$Gly^{8}Lys^{22}$ His^{37}-GLP-1(7-37); $Met^{8}Lys^{22}His^{37}$-GLP-1(7-37);$Gly^{8}Arg^{22}His^{37}$-GLP-1(7-37); $Val^{8}Arg^{22}His^{37}$-GLP-1(7-37); $Met^{8}Arg^{22}His^{37}$-GLP-1(7-37); $Gly^{8}His^{22}His^{37}$-GLP-1(7-37); $Val^{8}His^{22}His^{37}$-GLP-1(7-37); $Met^{8}His^{22}His^{37}$-GLP-1(7-37); $Gly^{8}His^{37}$-GLP-1(7-37); $Val^{8}His^{37}$-GLP-1(7-37); $Met^{8}His^{37}$-GLP-1(7-37);$Gly^{8}Asp^{22}$ His^{37}-GLP-1(7-37); $Val^{8}Asp^{22}His^{37}$-GLP-1(7-37); $Met^{8}Asp^{22}His^{37}$-GLP-1(7-37); Arg^{26}-GLP-1(7-36)-amide; Arg^{34}-GLP-1(7-36)-amide; Lys^{36}-GLP-1(7-36)-amide; $Arg^{26,34}Lys^{36}$-GLP-1(7-36)-amide; $Arg^{26,34}$-GLP-1(7-36)-amide; $Arg^{26,34}Lys^{40}$-GLP-1(7-36)-amide; $Arg^{26}Lys^{36}$-GLP-1(7-36)-amide; $Arg^{34}Lys^{36}$-GLP-1(7-36)-amide; Gly^{8}-GLP-1(7-36)-amide; Val^{8}-GLP-1(7-36)-amide; Met^{8}-GLP-1(7-36)-amide;$Gly^{8}Asp^{22}$-GLP-1(7-36)-amide; $Gly^{8}Glu^{22}His^{37}$-GLP-1(7-36)-amide; $Val^{8}Asp^{22}$-GLP-1(7-36)-amide; $Met^{8}Asp^{22}$-GLP-1(7-36)-amide;$Gly^{8}Glu^{22}$-GLP-1(7-36)-amide; $Val^{8}Glu^{22}$-GLP-1(7-36)-amide; $Met^{8}Glu^{22}$-GLP-1(7-36)-amide; $Gly^{8}Lys^{22}$-GLP-1(7-36)-amide; $Val^{8}Lys^{22}$-GLP-1(7-36)-amide; $Met^{8}Lys^{22}$-GLP-1(7-36)-amide; $Gly^{8}His^{22}His^{37}$-GLP-1(7-36)-amide; $Gly^{8}Arg^{22}$-GLP-1(7-36)-amide; $Val^{8}Arg^{22}$-GLP-1(7-36)-amide; $Met^{8}Arg^{22}$-GLP-1(7-36)-amide;$Gly^{8}His^{22}$-GLP-1(7-36)-amide; $Val^{8}His^{22}$-GLP-1(7-36)-amide; $Met^{8}His^{22}$-GLP-1(7-36)-amide;His^{37}-GLP-1(7-36)-amide; $Val^{8}Arg^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}Arg^{22}His^{37}$-GLP-1(7-36)-amide; $Gly^{8}His^{37}$-GLP-1(7-36)-amide; $Val^{8}His^{37}$-GLP-1(7-36)-amide; $Met^{8}His^{37}$-GLP-1(7-36)-amide;$Gly^{8}Asp^{22}$ His^{37}-GLP-1(7-36)-amide; $Val^{8}Asp^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}Asp^{22}His^{37}$-GLP-1(7-36)-amide; $Val^{8}Glu^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}Glu^{22}His^{37}$-GLP-1(7-36)-amide;$Gly^{8}Lys^{22}$ His^{37}-GLP-1(7-36)-amide; $Val^{8}Lys^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}Lys^{22}His^{37}$-GLP-1(7-36)-amide;$Gly^{8}Arg^{22}His^{37}$-GLP-1(7-36)-amide; $Val^{8}His^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}His^{22}His^{37}$-GLP-1(7-36)-amide; and derivatives thereof.

In yet another embodiment the GLP-1 agonist is selected from the group consisting of $Val^{8}Trp^{19}Glu^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}Val^{25}$-GLP-1(7-37), $Val^{8}Tyr^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Leu^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Tyr^{18}Glu^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}His^{37}$-GLP-1(7-37), $Val^{8}Glu^{22}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Val^{25}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Ile^{33}$-GLP-1(7-37), $Val^{8}Glu^{22}Val^{25}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Val^{25}$-GLP-1(7-37), analogues thereof and derivatives of any of these.

In yet another embodiment the GLP-1 agonist is exendin-4 or exendin-3, an exendin-4 or exendin-3 analogue or a derivative of any of these.

Examples of exendins as well as analogues, derivatives, and fragments thereof to be included within the present invention are those disclosed in WO 97/46584, US 5,424,286 and WO 01/04156. US 5,424,286 describes a method for stimulating insulin release with an exendin polypeptide. The exendin polypeptides disclosed include HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGX; wherein X = P or Y, and HX1X2GTFITSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS; wherein X1X2 = SD (exendin-3) or GE (exendin-4)). WO 97/46584 describes truncated versions of exendin peptide(s). The disclosed peptides increase secretion and biosynthesis of insulin, but reduce those of glucagon. WO 01/04156 describes exendin-4 analogues and derivatives as well as the preparation of these molecules. Exendin-4 analogues stabilized by fusion to serum albumin or Fc portion of an Ig are disclosed in WO 02/46227.

In one embodiment, the exendin-4 analogue is HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPSKKKKKK-amide.

Where the peptide to be included in the formulation of the invention is a GLP-1 agonist, the GLP-1 agonist is present in a concentration from about 0.1 mg/ml to about 100 mg/ml, more preferably in a concentration from about 0.1 mg/ml to about 50 mg/ml, and most preferably in a concentration of from about 0.1 mg/ml to about10 mg/ml.

In another embodiment, the peptide to be included in the formulation of the invention is insulin , where "insulin" is understood to mean human insulin, [where "human insulin" means insulin having the amino acid sequence shown in DSHW Nicol and LF Smith: Nature, (1960) 4736:483-485, which is hereby incorporated by reference], human insulin analogs, human insulin derivatives or mixtures thereof, where examples of insulin analogs and derivatives are those disclosed in EP 0 792 290 (Novo Nordisk A/S), EP 0 214 826 and EP 0 705 275 (Novo Nordisk A/S), US 5,504,188 (Eli Lilly), EP 0 368 187 (Aventis), US patents 5,750,497 and 6,011,007, EP 375437 and EP 383472 and where such insulins may include, but are not limited to, NPH insulin, Lys ß29 (Nϵ-tetradecanoyl) des(B30) human insulin, Lys^{B29}-(N$^{\epsilon}$-(γ-glutamyl-N$^{\alpha}$-lithocholyl) des(B30) human insulin, N^{LB29}-octanoyl insulin, 30/70 mixtures of prompt insulin zinc (SemiLente®) with extended insulin zinc (Ultralente®), sold commercially as Lente®, insulin glargine (Lantus®) or extended insulin zinc (Ultralente®), Lys^{B28} Pro^{B29} human insulin (Humalog®) , Asp^{B28} human insulin, insulin aspart (Novolog®), or a 30/70 mixture of insulin aspart and insulin aspart protamine (NovoMix®) .

In one embodiment, the insulin is a derivative of human insulin or a human insulin analogue where the derivative contains at least one lysine residue and a lipophilic substituent is attached to the epsilon amino group of the lysine residue.

In one embodiment, the lysine residue to which the lipophilic substituent is attached is present at position B28 of the insulin peptide.

In an alternative embodiment, the lysine residue to which the lipophilic substituent is attached is present at position B29 of the insulin peptide.

In yet another embodiment, lipophilic substituent is an acyl group corresponding to a carboxylic acid having at least 6 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group, branched or unbranched, which corresponds to a carboxylic acid having a chain of carbon atoms 8 to 24 atoms long.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a fatty acid having at least 6 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 6 to 24 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 8 to 12 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 10 to 16 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an oligo oxyethylene group comprising up to 10, preferably up to 5, oxyethylene units.

In another preferred embodiment, the lipophilic substituent is an oligo oxypropylene group comprising up to 10, preferably up to 5, oxypropylene units.

In one preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys; Phe^{B1} may be deleted; the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms; and 2-4 Zn^{2+} ions may be bound to each insulin hexamer with the proviso that when B30 is Thr or Ala and A21 and B3 are both Asn, and Phe^{B1} is not deleted, then 2-4 Zn^{2+} ions are bound to each hexamer of the insulin derivative.

In another preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded

for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys, with the proviso that if the B30 amino acid residue is Ala or Thr, then at least one of the residues A21 and B3 is different from Asn; Phe^{B1} may be deleted; and the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms.

In another preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys; Phe^{B1} may be deleted; the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms; and 2-4 Zn^{2+} ions are bound to each insulin hexamer.

Where the peptide to be included in the formulation of the invention is an insulin, the insulin is present in a concentration from about 0.5 mg/ml to about 20 mg/ml, more preferably in a concentration from about 1 mg/ml to about 15 mg/ml.

In another embodiment, the peptide to be included in the formulations of the invention is hGH or Met-hGH.

Where the peptide to be included in the formulation of the invention is hGH or Met-hGH, the hGH or Met-hGH is present in a concentration from about 0.5 mg/ml to about 50 mg/ml, more preferably in a concentration from about 1 mg/ml to about 10 mg/ml.

In yet another embodiment, the peptide to be included in the formulations of the invention is GLP-2 or an analogue or derivative thereof.

Where the peptide to be included in the formulation of the invention is GLP-2 or an analogue or derivative thereof, the GLP-2 or an analogue or derivative thereof is present in a concentration from about 1 mg/ml to about 100 mg/ml, more preferably in a concentration from about 1 mg/ml to about 10 mg/ml.

In yet a further embodiment, the peptide to be included in the formulations of the invention is Factor VII or Factor VIIa or an analogue or derivative thereof.

Where the peptide to be included in the formulation of the invention is Factor VII or Factor VIIa or an analogue or derivative thereof, the Factor VII or Factor VIIa or an analogue or derivative thereof is present in a concentration from about 0.1 mg/ml to about 10 mg/ml, more preferably in a concentration from about 0.5 mg/ml to about 5 mg/ml.

In one embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 1 to about 50 mg/ml.

In another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 5 to about 25 mg/ml.

In yet another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 8 to about 16 mg/ml.

In yet a further embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 13 to about 15 mg/ml.

In still another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 13.5 to about 14.5 mg/ml.

In another embodiment of the invention, the formulation has a pH in the range from about 7.0 to about 9.5 where the term "about" as used in connection with pH means + or – 0.1 pH units from the stated number.

In a further embodiment of the invention, the formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the formulation has a pH in the range from about 7.2 to about 8.0.

In a further embodiment of the invention, the formulation has a pH in the range from about 7.0 to about 8.3.

In yet a further embodiment of the invention, the formulation has a pH in the range from about 7.3 to about 8.3.

In a preferred embodiment of the invention, the formulations contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

Where a buffer is to be included in the formulations of the invention, the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, or mixtures thereof. Each one of these specific buffers constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the buffer is glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate or mixtures thereof.

Where a pharmaceutically acceptable preservative is to be included in the formulations of the invention, the preservative is selected from the group consisting of phenol, m-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, or mixtures thereof. Each one of these specific preservatives constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the preservative is phenol or m-cresol.

In a further embodiment of the invention the preservative is present in a concentration from about 0.1 mg/ml to about 50 mg/ml, more preferably in a concentration from about 0.1 mg/ml to about 25 mg/ml, and most preferably in a concentration from about 0.1 mg/ml to about 10 mg/ml

The use of a preservative in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further embodiment of the invention the formulation may further comprise a chelating agent where the chelating agent may be selected from salts of ethlenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof. Each one of these specific chelating agents constitutes an alternative embodiment of the invention.

In a further embodiment of the invention the chelating agent is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 0.1mg/ml to 2mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 2mg/ml to 5mg/ml.

The use of a chelating agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further embodiment of the invention the formulation may further comprise a stabiliser selected from the group of high molecular weight polymers or low molecular compounds where such stabilizers include, but are not limited to, polyethylene glycol (e.g. PEG 3350), polyvinylalcohol (PVA), polyvinylpyrrolidone, carboxymethylcellulose, different salts (e.g. sodium chloride), L-glycine, L-histidine, imidazole, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and mixtures thereof. Each one of these specific stabilizers constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the stabiliser is selected from the group consisting of L-histidine, imidazole and arginine.

In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1mg/ml to 50mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 5mg/ml to 10mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0mg/ml to 20mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration

from 20mg/ml to 30mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 30mg/ml to 50mg/ml.

In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1mg/ml to 50mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 5mg/ml to 10mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 10mg/ml to 20mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 20mg/ml to 30mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 30mg/ml to 50mg/ml.

The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further embodiment of the invention the formulation of the invention may further comprise a surfactant where a surfactant may be selected from a detergent, ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, such as 188 and 407, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives such as alkylated and alkoxylated derivatives (tweens, e.g. Tween-20, or Tween-80), monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, glycerol, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids, glycerophospholipids (lecithins, kephalins, phosphatidyl serine), glyceroglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, docusate calcium, docusate potassium, SDS (sodium dodecyl sulfate or sodium lauryl sulfate), dipalmitoyl phosphatidic acid, sodium caprylate, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (e.g. 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, zwitterionic surfactants (e.g. N-alkyl-

N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (e.g. cetyl-trimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl β-D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35), fusidic acid derivatives- (e.g. sodium tauro-dihydrofusidate etc.), long-chain fatty acids and salts thereof C6-C12 (eg. oleic acid and caprylic acid), acylcarnitines and derivatives, N^{α}-acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N^{α}-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N^{α}-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof. Each one of these specific surfactants constitutes an alternative embodiment of the invention.

The use of a surfactant in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

The formulations of the invention may be prepared by conventional techniques, *e.g.* as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product..

As mentioned above, in a preferred embodiment, the formulations of the invention-contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

In one embodiment, the method for preparing such a peptide formulation comprises:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;
b) preparing a second solution by dissolving the peptide in water;
c) mixing the first and second solutions; and
d) adjusting the pH of the mixture in c) to the desired pH.

In another embodiment, the method for preparing such a peptide formulation comprises:

a) preparing a first solution by dissolving preservative and buffer in water;
b) adding propylene glycol to the first solution;

c) mixing the first solution with a second solution containing peptide dissolved in water; and

d) adjusting the pH of the mixture in c) to the desired pH.

In yet another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a solution by dissolving preservative, buffer and propylene glycol in water;

b) adding the peptide to the solution of step a); and

c) adjusting the pH of the solution of step b) to the desired pH.

As the formulations of the invention are optimal for production and for use in injection devices since they exhibit reduced deposits of production equipment and reduced clogging of injection devices, the above methods of production can be used to produce peptide formulations suitable for use in production and/or for use in injection devices.

The formulations of the invention are suitable for administration to a mammal, preferably a human. The route of administration of the formulations of the invention may be any route which effectively transports the peptide contained in the formulation to the appropriate or desired site of action, such as oral, nasal, buccal, pulmonal, transdermal or parenteral.

Due to the ability of propylene glycol to reduce clogging of injection devices when compared to other isotonic agents and to mannitol in particular, in a preferred embodiment, the formulations of the invention are to be administered parenterally to a patient in need thereof. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump.

A further option is a composition which may be a powder or a liquid for the administration of the formulation in the form of a nasal or pulmonal spray. As a still further option, the formulation can also be administered transdermally, *e.g.* from a patch, optionally a iontophoretic patch, or transmucosally, *e.g.* bucally. The above-mentioned possible ways to administer the formulations of the invention are not to be considered as limiting the scope of the invention.

Of course, it is understood that depending on the peptide or peptides included in the formulations of the invention, the formulations may be used in methods of treatment of diseases or conditions for which use of the peptide is indicated. One skilled in the art would understand that when used in such methods of treatment, the formulations would have to be administered

in amount effective to treat the condition or disease for which the peptide was being administered where an "effective amount" or an "amount...effective" is understood to mean a dosage which is sufficient in order for the treatment of the patient with the disease or condition to be treated to be effective compared to treatment without the administered dosage. It is to be understood that "an effective amount" is the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, the condition or disease to be treated (e.g. diabetes, obesity, weight loss, gastric ulcers), patient-related factors (e.g. weight, health, age, etc.), presence of co-administered medications (e.g. insulin), time of administration, or other factors known to a medical practitioner.

The present invention also relates to a method for reducing deposits on production equipment during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment as described in the Examples.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.3.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.3 to about 8.3.

The present invention also relates to a method for reducing deposits in the final product during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.3.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.3 to about 8.3.

The present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study as described in the Examples.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

All scientific publications and patents cited herein are specifically incorporated by reference. The following examples illustrate various aspects of the invention but are in no way intended to limit the scope thereof.

EXAMPLES

EXAMPLE 1

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxx

As laboratory experiments have shown that with regards to clogging of needles and deposits on needles, formulations without peptide ("placebo") give the same conclusions as formulations with peptide at 0.3-5.0 mg/ml, the screening studies in Example 1 have been done using placebo except where indicated otherwise.

Preparation of Formulations With Different Isotonic Agents

Preservative (5.5 mg/ml phenol) and buffer 1.24 mg/ml disodium hydrogen phosphate, dihydrate) were dissolved in water and the isotonic agent was added while stirring. pH was adjusted to pH 7.9 using Sodium Hydroxide and/or Hydrochloric acid. Finally, the formulation was

filtered through a 0.22 µm filter. The isotonic agents tested in each formulation and their concentrations are shown in Table 1.

Table 1 Composition of the tested formulations

Formulation no.	Tonicity modifier
1	Glucose monohydrate (38.0 mg/ml)
2	Laktose monohydrate (65.0 mg/ml)
3	Maltose (67.2 mg/ml)
4	Glycine (15.1 mg/ml)
5	Polyethylenglycol 400 (77.5 mg/ml)
6	L-arginin (24.6 mg/ml)
7	Myo-Inositol (35.2 mg/ml)
8	Propylene glycol (13.7 mg/ml)
9	Dimethylsulfon (18 mg/ml)
10	Mannitol (35.9 mg/ml)
11	Sorbitol (39.5 mg/ml)
12	Xylitol (39.5 mg/ml)
13	Sucrose (79.1 mg/ml
14	Glycerol (16 mg/ml)

Osmolarity

The osmolarity of the different placebo formulations was determined and the results are shown in Table 2.

An isotonic solution has an osmolarity of around 0.286 osmol/L. As can be seen from Table 2 three of the formulations (PEG 400, sucrose and xylitol) are more than 20% from being isotonic (0.229-0.343 osmol/l), however for these kind of experiments the osmolarity is not expected to influence the results, though, the tonicity of the formulations should be adjusted in future experiments.

Table 2. The measured osmolarity of the formulations

Formulation no.	Isotonic agent	Osmolarity
1	Glucose monohydrate (38.0 mg/ml)	0.315
2	Laktose monohydrate (65.0 mg/ml)	0.283
3	Maltose (67.2 mg/ml)	0.306
4	Glycine (15.1 mg/ml)	0.286
5	Polyethylenglykol 400 (77.5 mg/ml)	0.370
6	L-arginin(24.6 mg/ml)	0.318
7	Myo-Inositol (35.2 mg/ml)	0.285
8	Propylene glycol (13.7 mg/ml)	0.268
9	Dimethylsulfon (18 mg/ml)	0.274
10	Mannitol (35.9 mg/ml)	0.284
11	Sorbitol (39.5 mg/ml)	0.310
12	Xylitol (39.5 mg/ml)	0.351
13	Sucrose (79.1 mg/ml	0.346
14	Glycerol (16 mg/ml)	0.262

Drop test

A droplet of each formulation is placed on a microscope slide and let to dry. The deposit is visually examined by eye and light microscope.

A photograph of the dried droplets of some of the formulations is shown in Figure 1. In this figure it is clearly observed that mannitol cause deposits on the microscope slide when let to dry. No deposits were observed for sorbitol, xylitol, sucrose and glycerol. The droplet on the far right (Form 1) contains mannitol and Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

In Figure 2, the candidates causing the most deposits on the microscope slide are shown. For comparison glycerol, which does not cause deposits, is shown (mannitol, arginine, inositol).

Clogging test

In this test 10 NovoPens® 1.5 ml mounted with NovoFine 30® G (G 30 needle) were tested for each formulation, 5 of them placed in upright and 5 in horizontal position. The Pensystems were stored at room temperature in between testing. Each day the needle was examined for deposits and an air shot was performed prior to injection into a tissue. Degree of resistance and clogging, if any, was noted. Injections were made on a daily basis with the same needle, and this was done for 9 working days for all the formulations.

The results from the clogging test are shown in Table 3.

Table 3 Clogging test in NovoPen 1.5 using 30G NovoFine

Isotonic agent (no. of observa-tions)	Some resist-ance	Resist-ance	Much resist-ance	Clogged	Drop at top of needle	Dried drop at needle top	Gel-like drop on needle	Deposits on needle
Mannitol (90)	10	0	0	0	0	2	0	43
Glycerol (90)	13	0	0	0	1	0	3	0
Sucrose (90)	23	0	0	0	0	0	21	0
Propylene glycol (90)	20	0	0	0	0	0	0	0
PEG 400 (90)	25	1	0	0	12 (5 at needle)	0	0	0
arginin (90)	26	2	0	0	3 (2 at needle)	1	0	0
Xylitol (90)	14	0	0	0	5	0	0	0
Dimethyls ulfon (90)	21	0	0	0	4	0	0	0
sorbitol (90)	12	0	0	0	9	1	0	1
Myo-inositol (90)	20	1	2	6	6	0	0	47
Glucose (90)	32	11	5	0	16 (7 at needle)	1	0	(1 at needle)
glycine (90)	41	9	2	0	1 (2 at needle)	0	0	31 (2 at needle)
maltose (90)	35	8	7	4	16 (6 at needle)	0	0	1 (5 at needle)
laktose (90)	44	10	8	0	5	0	0	31 (2 at needle)

In Table 3 and in Figure 3 it was observed that inositol and maltose clogged the needle. For comparison glycerol which does not clog the needle is shown in Figure 3. In Figure 4, and in Table 3, it was observed that formulations containing glycine, lactose and mannitol gave rise to a lot of deposits on the needle. For glycine, the deposits were a droplet deposited down the needle, whereas for lactose and mannitol the deposits occurred at the top of the needle.

Simulated filling

1 L of each formulation was subjected to a simulated filling experiment which lasted for 24 hours. After 24 hours the filling equipment was inspected for the presence of deposits.

Based on the results from the simulated filling studies (data not shown), the placebo formulations can be divided into three categories. 1. Those isotonic agents that do not cause deposits on the filling equipment: Xylitol, glycerol, glucose monohydrate, maltose, PEG 400 and propylene glycol. 2. Those isotonic agent that cause few deposits and have superior filling properties compared to mannitol: Sorbitol, sucrose and glycine. 3. Those isotonic agent that are comparable or worse than mannitol: Mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

Conclusion

In the simulated filling experiment xylitol, glycerol, glucose, maltose, PEG 400, propylene glycol, sorbitol, sucrose and glycine were found to be suitable replacements candidates for mannitol. However, as glucose is a reducing saccharide, and therefore is able to initiate unwanted degradation in the formulation, this tonicity modifier is ruled out. Furthermore, maltose is ruled out due to clogging of needles. This leads to the following candidates: glycerol, xylitol, sorbitol, sucrose, glycine, propylene glycol and PEG 400, which are found to have suitable properties as replacements candidates for mannitol in peptide formulations with regards to drop test, clogging of needles and simulated filling.

However, on the basis of the following considerations, propylene glycol was chosen as the isotonic agent over the other candidates to be further investigated in head to head comparison studies with mannitol:

a. propylene glycol was observed to have no influence on the physical and chemical stability of Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations;

b. propylene glycol was observed to have no influence on antimicrobial preservative testing; and

c. use of propylene glycol would no require that further toxicity studies be tested

EXAMPLE 2

Comparison Of Mannitol and Propylene Glycol-Containing Placebo Formulations In Simulated Filling Studies and Simulated Use Studies

Preparation of Formulations

Preservative and buffer were dissolved in water and the isotonic agent was added while stirring. pH was adjusted to the aimed pH using Sodium Hydroxide and/or Hydrochloric acid. Finally, the formulation was filtered through a 0.22 µm filter. The compositions of the formulations were as follows:

Disodium hydrogen phosphate, dihydrate:	1.42 mg/ml
Phenol:	5.5 mg/ml
Propylene glycol or mannitol:	13.7 or 35.9 mg/ml
Water for Injection:	up to 1.0 ml.
pH: 7.90	

Simulated Filling Study

A simulated filling study lasting 24 hours was performed as described in Example 1 and after 24 hours, the filling equipment was inspected for the presence of deposits. No deposits were observed on the filling equipment for the propylene glycol formulation. By comparison, after 24 hours, a lot of deposits were observed on the filling equipment for the mannitol formulation (see Figure 6).

Simulated In Use Study

For the simulated in use study, a clogging test was conducted as described in Example 1. The same needle was used during the study period of ten working days and each day, the needle was inspected for the presence of deposits. Figure 7 shows photographs of needles dosed with the propylene glycol (top panel) or mannitol (bottom panel) containing formulations. Deposits on the needle were observed in 48% of the cases when mannitol was used as an isotonic agent whereas no deposits were observed when propylene glycol was used as the isotonic agent.

Example 3

Comparison of Propylene Glycol to Mannitol In Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) Containing Formulations

Preparation of Formulations

Preservative, isotonic agent (mannitol or propylene glycol) and buffer were dissolved in water and pH was adjusted to the desired pH. Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) was dissolved in water while stirring slowly. The two solutions were then mixed and pH adjusted to the desired pH using sodium hydroxide and/or hydrochloric acid. Finally, the formulation was filtered through a 0.22 µm filter. The compositions of the formulations were as follows:

Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) (6.25 mg/ml),
Disodium hydrogen phosphate, dihydrate (1.42 mg/ml),
Phenol (5.5 mg/ml),
mannitol or propylene glycol (35.9 or 14.0 mg/ml),
Water for Injection (up to 1.0 ml),
pH: 8.15

Simulated In Use Study

For the simulated in use study, a clogging test was conducted as described in Example 1 except that a G31 needle was used. The same G31 needle was used during the study period of ten working days and each day, the needle was inspected for the presence of deposits. Figure 7 shows photographs of needles with no deposits when dosed with the propylene glycol (bottom panel) or showing deposits when dosed with the mannitol (top panel) containing formulations.

For the mannitol containing formulation, clogging of the needle was observed in 1 out of 10 cases on day 4, 2 out of 10 cases on day 5, 3 out of 10 cases on day 8 and 4 out of 10 cases on day 9. By comparison, no clogging of needles was observed for the propylene glycol containing formulation.

It is believed that similar results to those obtained with the above-described propylene glycol-containing formulation would also be obtained if the pH was adjusted to 7.40, 7.70 or 7.90. In addition, additional formulations which could be tested include those having the following compositions:

Buffering agents: glycylglycine (1.32 mg/ml), L-Histidine (1.55 mg/ml), Hepes (2.38 mg/ml), or bicine (1.63 mg/ml)

Preservatives: phenol (5.0 or 5.5 mg/ml), benzylalcohol (18 mg/ml) or a mixture of m-cresol and phenol (2.5/2.0 mg/ml)

Propylene glycol: 14.0 or 14.3 mg.ml
Water for injection: up to 1.0 ml
pH: 7.40, 7.70, 7.90 or 8.15

Example 4

Influence of Peptide Concentration On Clogging of Needles

Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) formulations were prepared as described in Example 3 using peptide concentrations ranging from 0-5 mg/ml of Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37). The compositions of the formulations were as follows:

Liraglutide: 0, 0.3, 3 and 5 mg/ml
Disodium hydrogen phosphate, dihydrate: 0.71 mg/ml
Sodium dihydrogenphosphate, dihydrate: 0.62 mg/ml
Mannitol: 36.9 mg/ml
Phenol: 5.0 mg/ml
Water for injection: up to 1.0 ml
pH 7.40

A simulated in use study was conducted as in Example 3 except that a G30 needle was used and the results (data not shown) indicated that the clogging effect of the mannitol-containing formulations relative to the absence of clogging with the propylene glycol formulations was observed independent of the peptide concentration.

Example 5

Clogging of needles in Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations Containing Mannitol

Preparation Of Formulations

The Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin-containing formulation was prepared as follows:

a) Prepared a first solution by dissolving buffer, sodium chloride, preservatives (phenol and m-cresol) and mannitol in water

b) Prepared a second solution of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and zinc acetate dissolved in water

c) added the peptide-containing solution of step b) to the solution of step a); and

d) adjusted the pH of the solution to the desired pH

The composition of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin-containing formulation prepared in the above manner was as follows:

Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin (2400 nmol), Phenol (1.80 mg/ml), m-cresol (2.06 mg/ml), Mannitol (30.0 mg/ml), disodiumphosphate, dihydrate (0.890 mg/ml), Sodium chloride (1.17 mg/ml), Zinc acetate (65.4 ug/ml), water for injection (up to 1.0 ml), pH: 7.4

The NovoMix 30-containing formulation was prepared as follows:

a) Prepared a solution by dissolving buffer, sodium chloride, phenol, mannitol and sodium hydroxide in water

b) Prepared a solution of sodium chloride, phenol and mannitol in water

c) Prepared a solution of protamine sulphate in water

d) Prepared a solution of insulin, hydrochloric acid and zinc in water

e) Solutions b), c) and d) were mixed

f) Solution e) was added to the solution of step a)

g) Adjustedthe pH of the solution to the desired pH and crystallized at room temperature

h) Prepared a solution by dissolving m-cresol, phenol and mannitol in water

i) Solution h) is added to the crystalline fraction of step g); and

j) Adjusted the pH to the desired pH

The composition of the NovoMix 30-containing formulation prepared in the above manner was as follows:

Insulin aspart (100 units/ml), protamine sulphate (approx. 0.33 mg/ml), phenol (1.50 mg/ml), m-cresol (1.72 mg/ml), mannitol (30.0 mg/ml), disodiumphosphate dihydrate (1.25 mg/ml), sodium chloride (0.58 mg/ml), zinc (19.6 ug/ml), water for injection (up to 1.0 ml), pH: 7.3.

Results

A simulated in use study was conducted as described in Example 3 using G31 needles where 20 needles were investigated for 10 days. The results were as follows: Clogging of needles was observed for Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin on day 2 (5%), day 3 (70%) and on day 4 (100%). Clogging of needles for NovoMix 30 was observed on day 3 (5%), day 4 (10%), day 5 (35%), day 6 (40%), day 8 (50%), day 9 (55%) and day 10 (80%). Thus, the effect of mannitol on the clogging of needles is independent of the type of peptide included in the formulations since a comparable clogging effect was observed with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37), Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30.

Example 6

Testing of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations containing propylene glycol

The preparation and composition of the Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations will be as described in Example 5 except that mannitol will be replaced with a concentration of propylene glycol that assures tonicity. A simulated in use test will then be conducted as described in Example 5.

Based on the fact that the clogging effect of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 mannitol-containing formulations was similar to that observed with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) mannitol-containing formulations, it is believed that the effect of propylene glycol on the clogging effect of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30-containing formulations will be similar to that observed with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations.

Claims

1. A pharmaceutical formulation comprising at least one peptide and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.

2. The formulation according to claim 1, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

3. The formulation according to claim 1, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

4. The formulation according to claim 1, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

5. The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 9.5.

6. The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.

7. The formulation according to claim 1, wherein the pH of said formulation is about 7.3 to about 8.3.

8. The formulation according to claim 1, further comprising a preservative.

9. The formulation according to claim 8, wherein said preservative is present in a concentration from 0.1mg/ml to 20mg/ml.

10. The formulation according to claim 1, further comprising a buffer.

11. The formulation according to claim 10, wherein said buffer is selected from the group consisting of glycylglycine, L-histidine, Hepes, bicine and disodium phosphate dihydrate.

12. The formulation according to claim 1, wherein said peptide is a GLP-1 agonist.

13. The formulation according to claim 12, wherein said GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

14. The formulation according to claim 13, wherein said GLP-1 agonist is a derivative of GLP-1(7-36) or GLP-1(7-37) or a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, where said derivative has a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine.

15. The formulation according to claim 14, wherein said lipophilic substituent has from 8 to 40 carbon atoms.

16. The formulation according to claim 15, wherein said spacer is an amino acid.

17. The formulation according to claim 16, wherein said GLP-1 agonist is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

18. The formulation according to claim 12, wherein said GLP-1 agonist is selected from the group consisting of Gly^8-GLP-1(7-36)-amide, Gly^8-GLP-1(7-37), Val^8-GLP-1(7-36)-amide, Val^8-GLP-1(7-37), Val^8Asp^{22}-GLP-1(7-36)-amide, Val^8Asp^{22}-GLP-1(7-37) , Val^8Glu^{22}-GLP-1(7-36)-amide , Val^8Glu^{22}-GLP-1(7-37), Val^8Lys^{22}-GLP-1(7-36)-amide, Val^8Lys^{22}-GLP-1(7-37), Val^8Arg^{22}-GLP-1(7-36)-amide, Val^8Arg^{22}-GLP-1(7-37), Val^8His^{22}-GLP-1(7-36)-amide, Val^8His^{22}-GLP-1(7-37), Arg34GLP-1(7-37); Arg26,34,Lys36GLP-1(7-36); Arg26GLP-1(7-37); and Gly8,Arg26,34,Glu37,Lys38GLP-1(7-38) analogues thereof and derivatives of any of these.

19. The formulation according to claim 1, wherein said peptide is selected from insulin, an insulin analogue, a derivative of insulin or an insulin analogue or a mixture of any of the foregoing.

20. The formulation according to claim 19, wherein said peptide is an insulin derivative in which said derivative contains a lysine residue to which a lipophilic substituent of at least six carbon atoms is attached.

21. The formulation according to claim 20, wherein the insulin derivative is Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin.

22. The formulation according to claim 20, wherein said insulin derivative is N^{LB29}-octanoyl insulin.

23. The formulation according to claim 19, wherein said peptide is a 30/70 mixture of insulin aspart and insulin aspart protamine.

24. The formulation according to claim 1, wherein said peptide is human growth hormone (hGH) or Met-hGH.

25. The formulation according to claim 24, wherein said peptide is exendin 4, an exendin 4 analogue or a derivative of exendin 4 or an exendin 4 analogue.

26. The formulation according to claim 25, wherein said peptide is exendin 4.

27. The formulation according to claim 25, wherein said peptide is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPSKKKKKK-amide.

28. A method of preparing a peptide formulation suitable for use in an injection device, said method comprising preparing a formulation containing peptide and propylene glycol and optionally a buffer and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from about 7.0 to about 10.0.

29. The method according to claim 28, wherein said peptide, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;
b) preparing a second solution by dissolving the peptide in water;
c) mixing the first and second solutions; and
d) adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

30. The method according to claim 28, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

31. The method according to claim 28, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

32. The method according to claim 28, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

33. The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 9.5.

34. The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 8.0.

35. The method according to claim 28, wherein the pH of said formulation is about 7.2 to about 8.0.

36. A method for reducing deposits on production equipment during production of a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

37. The method according to claim 36, wherein the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

38. The method according to claim 36, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

39. A method for reducing deposits in the final product during production of a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

40. The method according to claim 39, wherein the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials

and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

41. The method according to claim 39. wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, glycerol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

42. A method for reducing the clogging of injection devices by a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

43. The method according to claim 42, wherein the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

44. The method according to claim 42, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

Abstract

The present invention relates to pharmaceutical formulations comprising a peptide and propylene glycol, to methods of preparing such formulations, and to uses of such formulations in the treatment of diseases and conditions for which use of the peptide contained in such formulations is indicated. The present invention further relates to methods for reducing the clogging of injection devices by a peptide formulation and for reducing deposits on production equipment during production of a peptide formulation.

FIGURE 1

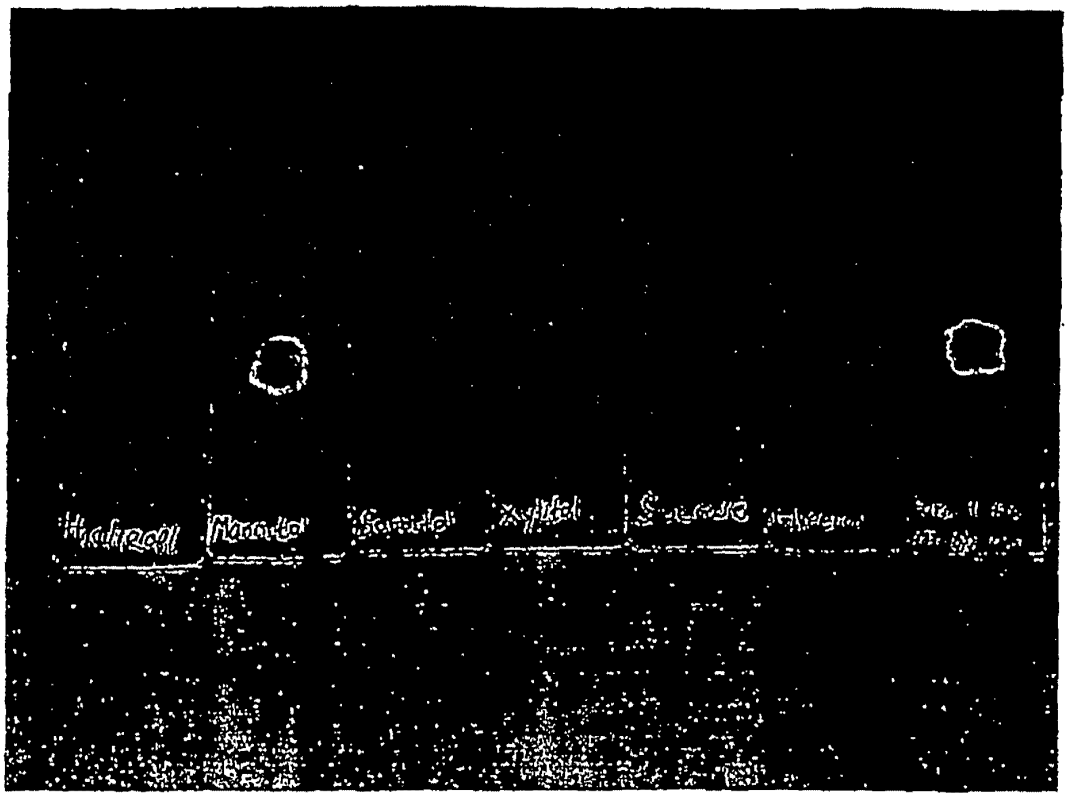
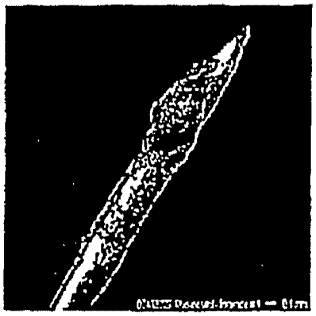


FIGURE 2

FIGURE 3

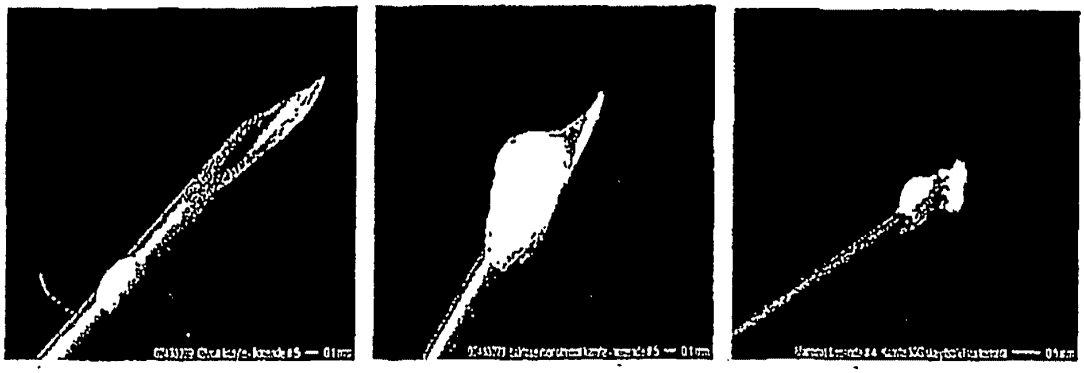


Myo-inositol

Maltose

Glycerol

FIGURE 4



Glycine Lactose Mannitol

FIGURE 5

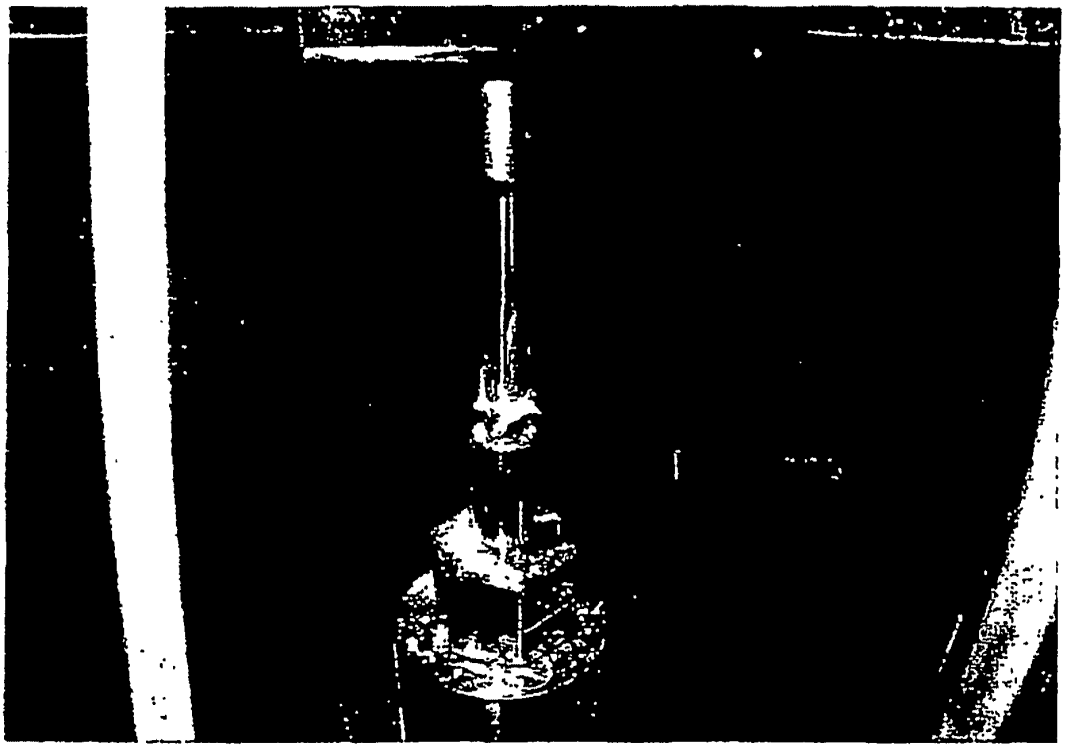


FIGURE 6

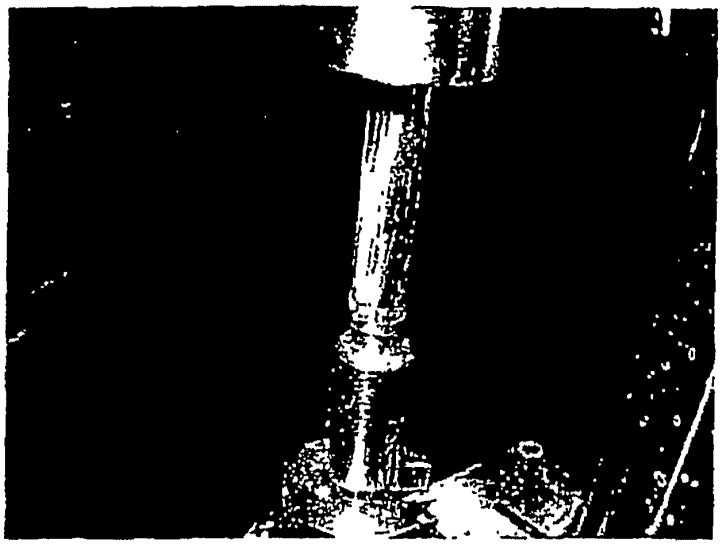
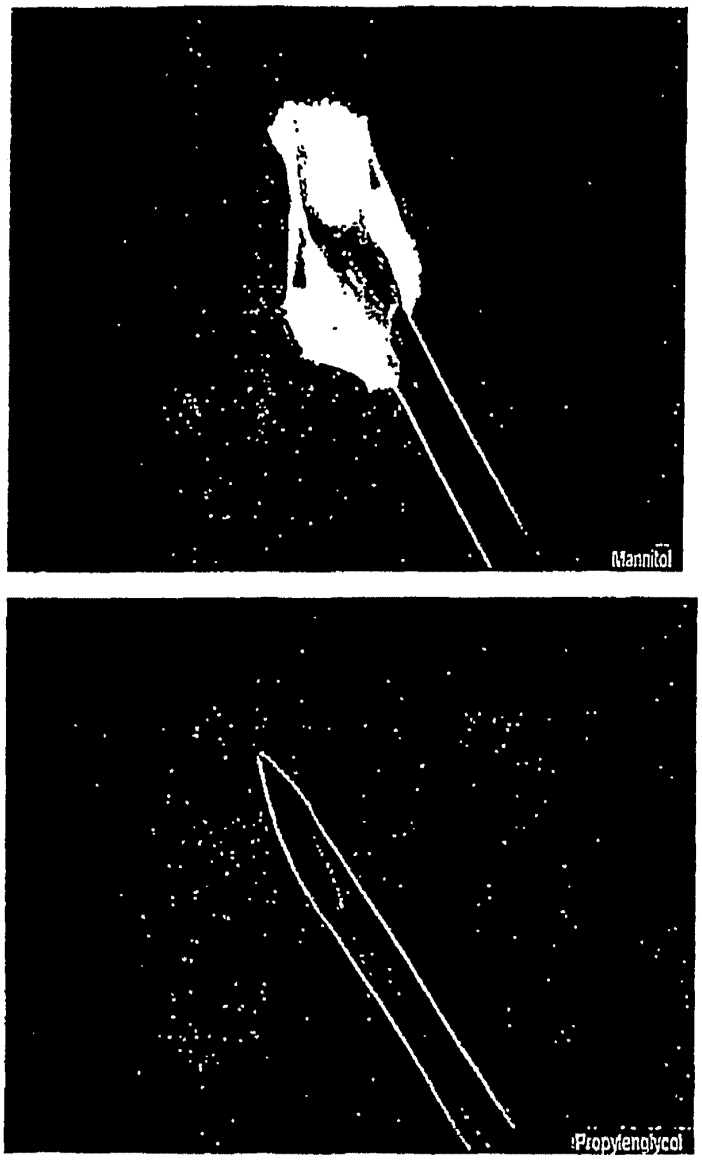


FIGURE 7



COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	Attorney's Docket Number: 6683.204-US

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

The specification of which (check only one item below):
[x] is attached hereto
[ ] was filed as United States application

Application No. To Be Assigned

on **May 17, 2006**
and was amended
on

[ ] was filed as PCT international application
Number
on
and was amended under PCT Article 19
on

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by an amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 of any provisional or foreign application(s) for patent or inventor's certificate or of any PCT international applications(s) for patent or inventor's certificate or of any PCT international applications(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR U.S. PROVISIONAL/FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicated "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
Denmark	PA 2003 01719	20 November 2003	[x] YES [ ] NO
United States of America	60/524,653	24 November 2003	[x] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

Attorney's Docket Number: **6683.204-US**

I hereby claim the benefit under Title 35, United States Code '120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this applications is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, '112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, '1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	Patented	Pending	Abandoned
PCT APPLICATIONS DESIGNATING THE U.S.				
APPLICATION NO.	FILING DATE	US SERIAL NUMBERS ASSIGNED (if any)		
PCT/DK2004/000792	18 November 04			x

POWER OF ATTORNEY: As a named inventor, I hereby appoint the attorney(s) and/or agent(s) associated with Customer Number 23650, including the following attorney(s) and/or agent(s), to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. Reza Green, Reg.No. 38,475; Richard W. Bork, Reg. No. 36,459; Marc A. Began, Reg. No. 48,829; Rosemarie R. Wilk-Orescan, Reg. No. 45,220; Len S. Smith, Reg. No. 43,139

Send Correspondence to: Reza Green, Esq.
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 0840

Direct Telephone Calls To:
Reza Green
(609) 987-5800

1	Full Name of Inventor	Family Name: **Pedersen**	First Given Name: **Tina**	Second Given Name: **Bjeldskov**
	Residence & Citizenship	City: **Ballerup**	State or Foreign Country: **Denmark**	Country of Citizenship: **Denmark**
	Post Office Address	Post Office Address: **Osterhojvej 50**	City: **Ballerup**	State & Zip Code/Country: **DK-2750/Denmark**
2	Full Name of Inventor	Family Name: **Bonde**	First Given Name: **Claude**	Second Given Name:
	Residence & Citizenship	City: **Lyngby**	State or Foreign Country: **Denmark**	Country of Citizenship: **Denmark**
	Post Office Address	Post Office Address: **Borgevej 41 B**	City: **Lyngby**	State & Zip Code/Country: **DK-2800/Denmark**
3	Full Name of Inventor	Family Name: **Engelund**	First Given Name: **Dorthe**	Second Given Name: **Kot**
	Residence & Citizenship	City: **Holte**	State or Foreign Country: **Denmark**	Country of Citizenship: **Denmark**
	Post Office Address	Post Office Address: **Gassehaven 39**	City: **Holte**	State & Zip Code/Country: **DK-2840/Denmark**
4	Full Name of Inventor	Family Name:	First Given Name:	Second Given Name:
	Residence & Citizenship	City:	State or Foreign Country:	Country of Citizenship:
	Post Office Address	Post Office Address:	City:	State & Zip Code/Country:

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)				Attorney's Docket Number: 6683.204-US
5	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country
6	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country
7	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country
8	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country
9	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 1	Signature of Inventor 2	Signature of Inventor 3
Date	Date	Date
Signature of Inventor 4	Signature of Inventor 5	Signature of Inventor 6
Date	Date	Date
Signature of Inventor 7	Signature of Inventor 8	Signature of Inventor 9
Date	Date	Date

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al.

Serial No.: TBA Group Art Unit: TBA

Filed: May 17, 2006 Examiner: TBA

SEQUENCE LISTING TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

Applicants enclose herewith the Sequence Listing for the above-captioned application and a 3.5" floppy disk containing the Sequence Listing. The content of the attached paper entitled "SEQUENCE LISTING" and of the accompanying identically labeled diskette is the same. Furthermore, the information contained in the attached "SEQUENCE LISTING" and the ASCII-encoded file is identical to the information in the specification as originally filed. No new matter is added.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: May 17, 2006

Richard W. Bork, Reg. No. 36,459
Novo Nordisk Inc.
Customer Number 23650
(609) 987-5800

Use the following customer number for all correspondence regarding this application.

23650
PATENT TRADEMARK OFFICE

SEQUENCE LISTING

<110> Novo Nordisk A/S

<120> Propylene glycol-containing peptide formulations which are optimal for production and for use in injection devices

<130> 6683.204-WO

<140> PCT/DK2004/000792
<141> 2004-11-18

<150> PA 2003 01719
<151> 2003-11-20

<160> 1

<170> PatentIn version 3.1

<210> 1
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<222> (44)..(44)
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<400> 1

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1               5                   10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Ser Lys Lys Lys Lys Lys Lys
        35                  40
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PTO/SB/06 (12-04)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875 Effective December 8, 2004

Application or Docket Number: 11/435,977

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	150.00		N/A	300.00
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	$250		N/A	$500
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	$100		N/A	$200
TOTAL CLAIMS (37 CFR 1.16(i))	44 minus 20 =	* 24	X$ 25 =		OR	X$50 =	1200
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	* 2	X100 =			X200 =	400
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			+180=			+360=	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2600

APPLICATION AS AMENDED – PART II

AMENDMENT A		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X$ 25 =		OR	X$50 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X100 =		OR	X200 =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					+180=		OR	+360=	
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X$ 25 =		OR	X$50 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X100 =		OR	X200 =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					+180=		OR	+360=	
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

05/22/2006 MAHMED1 00000004 141447 11435977

01 FC:1011	300.00	DA
02 FC:1111	500.00	DA
03 FC:1311	200.00	DA
04 FC:1201	400.00	DA
05 FC:1202	1200.00	DA

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/69033

APPLICATION DATA SHEET

Application Information	
Application Type::	*Continuation of International Application No. PCT/DK2004/000792 filed November 18, 2004*
Subject Matter::	Utility
Total Drawing Sheets::	7
Sequence submission?::	*Paper*
Computer Readable Form (CRF)?::	*Yes*
Number of copies of CRF::	*1*
Title::	**PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES**
Total Pages Specification::	34 pages of specification and 1 page of abstract
Attorney Docket Number::	6683.204-US
Request for Early Publication?::	No
Total Drawing Sheets::	7
Small Entity?::	No
Request for Non-Publication?::	No

Applicant Information	
Applicant Authority Type::	*Inventor*
Primary Citizenship Country::	Denmark
Status::	*Full Capacity*
Given Name::	Tina
Middle Name::	Bjeldskov
Family Name::	Pedersen
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Country of Residence::	Denmark
Street of mailing address::	Osterhojvej 50
City of mailing address::	Ballerup
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2750
Applicant Authority Type::	*Inventor*
Primary Citizenship Country::	Denmark
Status::	*Full Capacity*
Given Name::	Claude
Middle Name::	
Family Name::	Bonde
City of Residence::	Lyngby
Country of Residence::	Denmark
Street of mailing address::	Borgevej 41 B
City of mailing address::	Lyngby
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2800
Applicant Authority Type::	*Inventor*

Primary Citizenship Country::	Denmark
Status::	*Full Capacity*
Given Name::	Dorthe
Middle Name::	Kot
Family Name::	Engelund
City of Residence::	Holte
Country of Residence::	Denmark
Street of mailing address::	Gassehaven 39
City of mailing address::	Holte
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2840

Correspondence Information

Correspondence Customer Number::	23650
Phone Number::	609-987-5800
Fax Number::	609-919-7741
E-Mail Address::	REZG@Novonordisk.com TRAB@Novonordisk.com Patents@Novonordisk.com

Representative Information

Representative Customer Number::	23650

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	*Continuation of*	PCT/DK2004/000792	*11/18/04*
	And Claims Priority of	60/524,653	*11/24/03*

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::
DK (Denmark)	*PA 2003 01719*	*11/20/03*	Yes

Assignee Information

Assignee name::	Novo Nordisk A/S
Street of mailing address::	Novo Allé
City of mailing address::	Bagsvaerd
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al.

Application No.: 11/435,977 Group Art Unit: 1646

Filed: May 17, 2006 Examiner: TBA

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with 37 C.F.R. 1.56, 1.97 and 1.98, Applicants submit herewith references which they believe may be material to the patentability of this application and with respect to which there may be a duty to disclose in accordance with 37 C.F.R. 1.56.

While the references may be "material" under 37 C.F.R. 1.56, it is not intended to constitute an admission that the references are "prior art" unless specifically designated as such.

The filing of this Information Disclosure Statement shall not be construed as a representation that no material references other than those listed exist or that a search has been conducted.

The references are listed in Form PTO-1449 which is in accordance with the requirements of M.P.E.P. 609. A copy of the references is also enclosed.

The references are as follows:

1. WO 2005/046716
2. WO 93/23010
3. WO 95/13825
4. WO 99/16417
5. U.S. Patent No. 2002/0151467

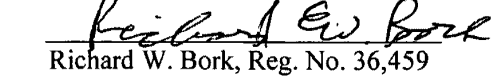
6. WO 03/013589
7. EP 1424077
8. U.S. Patent No.5206219
9. WO 95/22560
10. WO 95/05848
11. WO 02/067989
12. WO 92/19260
13. Sing, S et al – AAPS Pharmscitech – 2003 – Vol. 4 Part 3 – Pgs. 334-342

It is respectfully requested that these references be considered by the Patent and Trademark Office in its examination of the above-identified application and be made of record therein. The Examiner is also invited to contact the undersigned if there are any questions concerning this paper or the attached references.

The information disclosure statement submitted herewith is being filed **within** three months of the filing date of a national application or date of entry into the national stage of an international application or **before** the mailing date of a first Office action on the merits, or **before** the mailing date of a first Office action after the filing of a request for continued examination. Therefore, no fee is due. However, please charge any fees should they be required, to Novo Nordisk Inc. Deposit Account No. 14-1447.

Respectfully submitted,

Date: July 10, 2006



Richard W. Bork, Reg. No. 36,459
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

Use the following customer number for all correspondence regarding this application.

23650
PATENT TRADEMARK OFFICE

FORM PTO-1449 (Rev. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	Atty. Docket No. 6683.204-US	Serial No. 11/435,977
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	Applicant Pedersen et al.	
	Filing Date May 17, 2006	Group 1646

U.S. PATENT DOCUMENTS

EXAMINER		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		2002/0151467	12/21/00	Leung, F.K.			
		5206219	11/25/91	Applied Analytical Industries, INC			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		2005/046716	11/12/04	WO				
		93/23010	05/07/92	WO				
		95/13825	10/24/94	WO				
		99/16417	10/01/97	WO				
		03/013589	05/20/02	WO				
		1424077	05/20/02	EP				
		95/22560	02/21/95	WO				
		95/05848	08/23/94	WO				
		02/067989	01/08/02	WO				
		92/19260	05/07/91	WO				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

			Singh, S et al - Aaps Pharmscitech - 2003 - Vol. 4 - Part 3-Pgs.334-342

EXAMINER | DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

59-1-06

1746

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Serial No.: 11/435,977 Group Art Unit: 1646

Filed: May 17, 2006 Examiner: TBA

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

CERTIFICATE OF MAILING UNDER 37 CFR 1.8(a)

Date of Deposit: September 8, 2006
Express Mail Label No.: EV 450790449 US

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I hereby certify that the attached correspondence comprising:

1. Petition and Fee For Extension of Time (in duplicate)
2. Response to Notice to File Missing Parts (in duplicate)
3. Copy of Notice to File Missing Parts
4. Executed Combined Declaration and Power of Attorney (3 pages)
5. Substitute computer readable format (CRF) of Sequence Listing
6. Substitute paper copy of Sequence Listing
7. Certified copy of Priority Application No. PA 2003 01719

is being deposited with the United States Postal Service as **express** mail in an envelope addressed to:

MS: Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Rashida Haji
(name of person mailing paper)

Rashida Haji
(signature of person mailing paper)

Attorney Docket No.: 6683.204-US
Serial No.: 11/435,977
Filed: May 17, 2006
Inventors: Pedersen et al.
Express Mail Label No.: EV 450790449 US
Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Serial No.: 11/435,977 Group Art Unit: 1646

Filed: May 17, 2006 Examiner: TBA

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

RESPONSE TO NOTICE TO FILE MISSING PARTS

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notice to File Missing Parts dated June 12, 2006 (a copy thereof is attached hereto), Applicants submit the Combined Declaration and Power of Attorney signed and dated by Applicants for the above-captioned application.

Applicants also enclose certified copy of Danish application no. PA 2003 01719, priority of which is claimed under 35 U.S.C. 119.

Applicants also enclose herewith a substitute copy of the Sequence Listing for the above-captioned application and a substitute computer readable form (CRF) copy of the Sequence Listing.

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted in accordance with 37 CFR § 1.821(c) and (e), respectively, are the same.

Attorney Docket No.: 6683.204-US
Serial No.: 11/435,977
Filed: May 17, 2006
Inventors: Pedersen et al.
Express Mail Label No.: EV 450790449 US

Please charge the required fee, estimated to be $130.00, with this application and credit any overpayments to Novo Nordisk Inc., Deposit Account No. 14-1447. Please charge any additional fees, should they be required, to Deposit Account No. 14-1447. A duplicate of this sheet is enclosed.

Respectfully submitted,

Date: September 8, 2006

Richard W. Bork, Reg. No. 36,459
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

Use the following customer number for all correspondence regarding this application.

23650
PATENT TRADEMARK OFFICE

09-11-06

IPW

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US

CONFIRMATION NO. 7802

FORMALITIES LETTER

23650
NOVO NORDISK, INC.
PATENT DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

Date Mailed: 06/12/2006

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

09/12/2006 JBALINAN 00000058 141447 11435977 **FILED UNDER 37 CFR 1.53(b)**

01 FC:1051 130.00 DA

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.

- A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing." Applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d).

  Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

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B. Hayward

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PART 2 - COPY TO BE RETURNED WITH RESPONSE

RUBOR/BDHN/LBNS

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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US

CONFIRMATION NO. 7802

23650
NOVO NORDISK, INC.
PATENT DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

DOCKET (check off ✓) ☐
ATTY: TMB Docs 6/15/06

FORMALITIES LETTER

Date Mailed: 06/12/2006

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

JUN 15 2006

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B. Verbaleman 2.

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PART 1 - ATTORNEY/APPLICANT COPY

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

Attorney's Docket Number: 6683.304-US

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

The specification of which (check only one item below):
[x] is attached hereto
[ ] was filed as United States application

Application No. **11/435,977**

on **May 17, 2006**
and was amended
on

[ ] was filed as PCT international application
Number
on
and was amended under PCT Article 19
on

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by an amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 of any provisional or foreign application(s) for patent or inventor's certificate or of any PCT international applications(s) for patent or inventor's certificate or of any PCT international applications(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR U.S. PROVISIONAL/FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicated "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
Denmark	PA 2003 01719	20 November 2003	[x] YES [ ] NO
United States of America	60/524,653	24 November 2003	[x] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	Attorney's Docket Number: 6683.204-US

I hereby claim the benefit under Title 35, United States Code '120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this applications is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, '112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, '1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	Patented	Pending	Abandoned
PCT APPLICATIONS DESIGNATING THE U.S.				
APPLICATION NO.	FILING DATE	US SERIAL NUMBERS ASSIGNED (if any)		
PCT/DK2004/000792	18 November 04			x

POWER OF ATTORNEY: As a named inventor, I hereby appoint the attorney(s) and/or agent(s) associated with Customer Number 23650, including the following attorney(s) and/or agent(s), to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. Reza Green, Reg.No. 38,475; Richard W. Bork, Reg. No. 36,459; Marc A. Began, Reg. No. 48,829; Rosemarie R. Wilk-Orescan, Reg. No. 45,220; Len S. Smith, Reg. No. 43,139

Send Correspondence to: Reza Green, Esq. Novo Nordisk Pharmaceuticals, Inc. 100 College Road West Princeton, NJ 0840				Direct Telephone Calls To: Reza Green (609) 987-5800
1	Full Name of Inventor	Family Name **Pedersen**	First Given Name **Tina**	Second Given Name **Bjeldskov**
	Residence & Citizenship	City **Smørum**	State or Foreign Country **Denmark**	Country of Citizenship **Denmark**
	Post Office Address	Post Office Address **Kongehaven 9**	City **Smørum**	State & Zip Code/Country **DK-2765/Denmark**
2	Full Name of Inventor	Family Name **Bonde**	First Given Name **Claude**	Second Given Name
	Residence & Citizenship	City **Lyngby**	State or Foreign Country **Denmark**	Country of Citizenship **France**
	Post Office Address	Post Office Address **Borgevej 41 B**	City **Lyngby**	State & Zip Code/Country **DK-2800/Denmark**
3	Full Name of Inventor	Family Name **Engelund**	First Given Name **Dorthe**	Second Given Name **Kot**
	Residence & Citizenship	City **Holte**	State or Foreign Country **Denmark**	Country of Citizenship **Denmark**
	Post Office Address	Post Office Address **Gassehaven 39**	City **Holte**	State & Zip Code/Country **DK-2840/Denmark**
4	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)				Attorney's Docket Number: 6683.204-US
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	Post Office Address	Post Office Address	City	State & Zip Code/Country
6	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country
7	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country
8	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country
9	Full Name of Inventor	Family Name	First Given Name	Second Given Name
	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 1	Signature of Inventor 2	Signature of Inventor 3
Date 18-jul-2006	Date 02-Aug-2006	Date 24-jul-2006
Signature of Inventor 4	Signature of Inventor 5	Signature of Inventor 6
Date	Date	Date
Signature of Inventor 7	Signature of Inventor 8	Signature of Inventor 9
Date	Date	Date

SEQUENCE LISTING

<110> Novo Nordisk A/S
Pedersen, Tina
Bonde, Claude
Engelund, Dorthe

<120> Propylene glycol-containing peptide formulations

<130> 6683.204-US

<140> 11/435977
<141> 2006-05-17

<150> PCT/DK2004/000792
<151> 2004-11-18

<150> PA 2003 01719
<151> 2003-11-20

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<170> PatentIn version 3.3

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<223> Lysine at position 44 is amidated

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20 25 30

Ser Gly Ala Pro Pro Ser Lys Lys Lys Lys Lys Lys
35 40

Kongeriget Danmark

Patent application No.: PA 2003 01719

Date of filing: 20 November 2003

Applicant: (Name and address)
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Titlel: Propylene glycol-containing peptide formulations which are optimal for production and for use in injection devices

IPC: -

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

Patent- og Varemærkestyrelsen
Kongeriget Danmark

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

28 April 2006

Pia Høybye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations comprising a peptide and propylene glycol, to methods of preparing such formulations, and to uses of such formulations in the treatment of diseases and conditions for which use of the peptide contained in such formulations is indicated. The present invention further relates to methods for reducing the clogging of injection devices by a peptide formulation and for reducing deposits on production equipment during production of a peptide formulation.

BACKGROUND OF THE INVENTION

The inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known and one of the more common isotonic agents used in such formulations is mannitol. However, the present inventors have observed that mannitol causes problems during the production of peptide formulations as it crystallizes resulting in deposits in the production equipment and in the final product. Such deposits increase the need to clean the filling equipment during production of the formulation and this results in reduced production capability. In addition, such deposits may also result in reduced yield of the final product since vials/cartridges containing the peptide formulation may need to be discarded if particles are present. Finally, the present inventors have observed that in peptide formulations to be administered by injection, the presence of mannitol results in clogging of injection devices.

Accordingly, it is desirable to identify an alternative isotonic agent to mannitol for inclusion in peptide-containing formulations and in particular, for inclusion in peptide formulations which are administered by injection.

SUMMARY OF THE INVENTION

The present inventors have discovered that peptide formulations containing propylene glycol at certain concentrations exhibit reduced deposits in production equipment and in the final product and also exhibit reduced clogging of injection devices. The present compositions may be formulated with any peptide and are also physically and chemically stable thus rendering them shelf-stable and suitable for invasive (eg. injection, subcutaneous injection, intramuscular, intraveneous or infusion) as well as non-invasive (eg nasal, oral, pulmonary, transdermal or transmucosal e.g. buccal) means of administration.

The present invention therefore relates to a pharmaceutical formulation comprising a peptide and propylene glycol, where the propylene glycol is present in a concentration of 1-

100 mg/ml and the pH of the formulation is from 7-10. In a preferred embodiment, the pharmaceutical formulations of the invention further contain a buffer and a preservative.

The present invention also relates to methods for producing the pharmaceutical formulations of the invention.

In one embodiment, the method for preparing a peptide formulation comprises:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;

b) preparing a second solution by dissolving the peptide in water;

c) mixing the first and second solutions; and

d) adjusting the pH of the mixture in c) to the desired pH.

In another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a first solution by dissolving preservative and buffer in water;

b) adding propylene glycol to the first solution;

c) mixing the first solution with a second solution containing peptide dissolved in water; and

d) adjusting the pH of the mixture in c) to the desired pH.

In yet another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a solution by dissolving preservative, buffer and propylene glycol in water;

b) adding the peptide to the solution of step a); and

c) adjusting the pH of the solution of step b) to the desired pH.

The present invention further relates to methods of treatment using the pharmaceutical formulations of the invention where the compositions are administered in an amount effective to combat the disease, condition, or disorder for which administration of the peptide contained in the formulation is indicated.

In addition the present invention also relates to a method for reducing deposits on production equipment during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the

formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

The present invention also relates to a method for reducing deposits in the final product during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

The present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a photograph of dried droplets on microscope slides of from left to right, placebo (no peptide) formulations containing no isotonic agent (e only water, preservative and buffer), mannitol, sorbitol, xylitol, sucrose or glycerol as the isotonic agent with the far right slide containing mannitol with peptide Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

Figure 2 shows light microscopy pictures of from left to right, some of the dried droplets of placebo formulations containing mannitol, arginin, inositol or glycerol as the isotonic agent.

Figure 3 shows light microscopy pictures of clogged needles dosed with placebo formulations containing myoinositol, maltose or glycerol as the isotonic agent.

Figure 4 shows light microscopy pictures of deposits on needles dosed with placebo formulations containing glycine, lactose or mannitol as the isotonic agent.

Figure 5 shows filling equipment after 24 hours simulated filling with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) medium containing myo-inositol.

Figure 6 shows deposits on filling equipment after 24 hours simulated filling with a mannitol-containing placebo formulation.

Figure 7 shows deposits on G30 needles dosed with propylene glycol (left-hand panel) and mannitol (right-hand panel)-containing placebo formulations.

Figure 8 shows deposits on needles dosed with mannitol (top panel) and propylene glycol (bottom panel)-containing Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) formulations.

DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical formulation comprising a peptide or a mixture of peptides and propylene glycol where the final concentration of propylene glycol in the formulation is 1-100 mg/ml and the pH of the formulation is in the range of from 7-10.

The pharmaceutical formulations of the invention are found to be optimal for production because they exhibit reduced deposits in production equipment relative to formulations containing other isotonicity agents as measured by the simulated filling studies described in the Examples. In addition, the pharmaceutical formulations of the invention are found to be optimal for use in injection devices because they exhibit reduced clogging of the injection devices relative to formulations containing other isotonicity agents as measured by the simulated in use studies described in the Examples.

The formulations of the present invention may be formulated with any peptide where examples of such peptides include, but are not limited to, glucagon, human growth hormone (hGH), insulin, aprotinin, FactorVII, tissue plasminogen activator (TPA), FactorVIIa, FFR-FactorVIIa, heparinase, ACTH, Heparin Binding Protein, corticotropin-releasing factor, angiotensin, calcitonin, glucagon-like peptide-1, glucagon-like peptide-2, insulin-like growth factor-1, insulin-like growth factor-2, fibroblast growth factors, gastric inhibitory peptide, growth hormone-releasing factor, pituitary adenylate cyclase activating peptide, secretin, enterogastrin, somatostatin, somatomedin, parathyroid hormone, thrombopoietin, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, oxytocin, opiods, DPP IV, interleukins, immunoglobulins, complement inhibitors, serine protease

inhibitors, cytokines, cytokine receptors, PDGF, tumor necrosis factors, tumor necrosis factors receptors, growth factors and analogues as well as derivatives thereof where each of these peptides constitutes an alternative embodiment of the present invention.

In the present application, the designation "an analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either at the N-terminal end or at the C-terminal end of the parent peptide or both. Typically " an analogue" is a peptide wherein 6 or less amino acids have been substituted and/or added and/or deleted from the parent peptide, more preferably a peptide wherein 3 or less amino acids have been substituted and/or added and/or deleted from the parent peptide, and most preferably, a peptide wherein one amino acid has been substituted and/or added and/or deleted from the parent peptide.

In the present application, "a derivative" is used to designate a peptide or analogue thereof which is chemically modified by introducing an organic substituent e.g. ester, alkyl or lipophilic functionalities, on one or more amino acid residues of the peptide or analogue thereof.

In one embodiment, the peptide to be included in the formulation of the invention is a GLP-1 agonist where "a GLP-1 agonist" is understood to refer to any peptide which fully or partially activates the human GLP-1 receptor. In a preferred embodiment, the "GLP-1 agonist" is any peptide that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 µM, e.g. below 100 nM as measured by methods known in the art (see e.g. WO 98/08871) and exhibits insulinotropic activity, where insulinotropic activity may be measured in vivo or in vitro assays known to those of ordinary skill in the art. For example, the GLP-1 agonist may be administered to an animal and the insulin concentration measured over time.

Methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S) and examples of suitable GLP-1 analogues and derivatives which can be used according to the present invention includes those referred to in WO 99/43705 (Novo Nordisk A/S), WO 99/43706 (Novo Nordisk A/S), WO 99/43707 (Novo Nordisk A/S), WO 98/08871 (analogues with lipophilic substituent) and in WO 02/46227 (analogues fused to serum albumin or to Fc portion of an Ig).(Novo Nordisk A/S), WO 99/43708 (Novo Nordisk A/S), WO 99/43341 (Novo Nordisk A/S), WO 87/06941 (The General Hospital Corporation), WO 90/11296 (The General Hospital Corporation), WO 91/11457 (Buckley et al.), WO 98/43658 (Eli Lilly & Co.), EP 0708179-A2 (Eli Lilly & Co.), EP 0699686-A2 (Eli Lilly & Co.), WO 01/98331 (Eli Lilly & Co).

In one embodiment, the GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

In one embodiment, the GLP-1 agonist is a derivative of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, which comprises a lipophilic substituent.

In this embodiment of the invention, the GLP-1 derivative preferably has three lipophilic substituents, more preferably two lipophilic substituents, and most preferably one lipophilic substituent attached to the parent peptide (ie GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue), where each lipophilic substituent(s) preferably has 4-40 carbon atoms, more preferably 8-30 carbon atoms, even more preferably 8-25 carbon atoms, even more preferably 12-25 carbon atoms, and most preferably 14-18 carbon atoms.

In one embodiment, the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

In another embodiment, the lipophilic substituent is a straight-chain or branched alkyl group.

In yet another embodiment, the lipophilic substituent is an acyl group of a straight-chain or branched fatty acid. Preferably, the lipophilic substituent is an acyl group having the formula $CH_3(CH_2)_nCO$-, wherein n is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-. In a more preferred embodiment, the lipophilic substituent is tetradecanoyl. In a most preferred embodiment, the lipophilic substituent is hexadecanoyl.

In a further embodiment of the present invention, the lipophilic substituent has a group which is negatively charged such as a carboxylic acid group. For example, the lipophilic substituent may be an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid of the formula $HOOC(CH_2)_mCO$-, wherein m is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- or $HOOC(CH_2)_{22}CO$-.

In the GLP-1 derivatives of the invention, the lipophilic substituent(s) contain a functional group which can be attached to one of the following functional groups of an amino acid of the parent GLP-1 peptide:

(a) the amino group attached to the alpha-carbon of the N-terminal amino acid,

(b) the carboxy group attached to the alpha-carbon of the C-terminal amino acid,

(c) the epsilon-amino group of any Lys residue,

(d) the carboxy group of the R group of any Asp and Glu residue,

(e) the hydroxy group of the R group of any Tyr, Ser and Thr residue,

(f) the amino group of the R group of any Trp, Asn, Gln, Arg, and His residue, or

(g) the thiol group of the R group of any Cys residue.

In one embodiment, a lipophilic substituent is attached to the carboxy group of the R group of any Asp and Glu residue.

In another embodiment, a lipophilic substituent is attached to the carboxy group attached to the alpha-carbon of the C-terminal amino acid.

In a most preferred embodiment, a lipophilic substituent is attached to the epsilon-amino group of any Lys residue.

In a preferred embodiment of the invention, the lipophilic substituent is attached to the parent GLP-1 peptide by means of a spacer. A spacer must contain at least two functional groups, one to attach to a functional group of the lipophilic substituent and the other to a functional group of the parent GLP-1 peptide.

In one embodiment, the spacer is an amino acid residue except Cys or Met, or a dipeptide such as Gly-Lys. For purposes of the present invention, the phrase "a dipeptide such as Gly-Lys" means any combination of two amino acids except Cys or Met, preferably a dipeptide wherein the C-terminal amino acid residue is Lys, His or Trp, preferably Lys, and the N-terminal amino acid residue is Ala, Arg, Asp, Asn, Gly, Glu, Gln, Ile, Leu, Val, Phe, Pro, Ser, Tyr, Thr, Lys, His and Trp. Preferably, an amino group of the parent peptide forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

Preferred spacers are lysyl, glutamyl, asparagyl, glycyl, beta-alanyl and gamma-aminobutanoyl, each of which constitutes an individual embodiment. Most preferred spacers are glutamyl and beta-alanyl. When the spacer is Lys, Glu or Asp, the carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ε-amino group of Lys and the lipophilic substituent. In one embodiment, such a further spacer is succinic acid which forms an amide bond with the ε-amino group of Lys and with an amino group present in the lipophilic substituent. In another embodiment such a further spacer is Glu or Asp which forms an amide bond with the ε-amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent, that is, the lipophilic substituent is a N^{ε}-acylated lysine residue.

In another embodiment, the spacer is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, which spacer forms a bridge between an amino

group of the parent peptide and an amino group of the lipophilic substituent. Preferably, the spacer is succinic acid.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_pNH\text{-}CO(CH_2)_qCO\text{-}$, wherein p is an integer from 8 to 33, preferably from 12 to 28 and q is an integer from 1 to 6, preferably 2.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_rCO\text{-}NHCH(COOH)(CH_2)_2CO\text{-}$, wherein r is an integer from 4 to 24, preferably from 10 to 24.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_sCO\text{-}NHCH((CH_2)_2COOH)CO\text{-}$, wherein s is an integer from 4 to 24, preferably from 10 to 24.

In a further embodiment, the lipophilic substituent is a group of the formula $COOH(CH_2)_tCO\text{-}$ wherein t is an integer from 6 to 24.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_uCH_3$, wherein u is an integer from 8 to 18.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_vCO\text{-}NH\text{-}(CH_2)_z\text{-}CO$, wherein v is an integer from 4 to 24 and z is an integer from 1 to 6.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}COCH((CH_2)_2COOH)NH\text{-}CO(CH_2)_wCH_3$, wherein w is an integer from 10 to 16.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_2CH(COOH)NHCO(CH_2)_xCH_3$, wherein x is zero or an integer from 1 to 22, preferably 10 to 16.

In yet another embodiment the GLP-1 agonist is Arg^{34}, $Lys^{26}(N^{\varepsilon}\text{-}(\gamma\text{-}Glu(N^{\alpha}\text{-}hexadecanoyl)))$-GLP-1(7-37).

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Gly^8-GLP-1(7-36)-amide, Gly^8-GLP-1(7-37), Val^8-GLP-1(7-36)-amide, Val^8-GLP-1(7-37), Val^8Asp^{22}-GLP-1(7-36)-amide, Val^8Asp^{22}-GLP-1(7-37) , Val^8Glu^{22}-GLP-1(7-36)-amide , Val^8Glu^{22}-GLP-1(7-37), Val^8Lys^{22}-GLP-1(7-36)-amide, Val^8Lys^{22}-GLP-1(7-37), Val^8Arg^{22}-GLP-1(7-36)-amide, Val^8Arg^{22}-GLP-1(7-37), Val^8His^{22}-GLP-1(7-36)-amide, Val^8His^{22}-GLP-1(7-37), analogues thereof and derivatives of any of these.

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Arg^{26}-GLP-1(7-37); Arg^{34}-GLP-1(7-37); Lys^{36}-GLP-1(7-37); $Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Arg^{26,34}$-GLP-1(7-37); $Arg^{26,34}Lys^{40}$-GLP-1(7-37); $Arg^{26}Lys^{36}$-GLP-1(7-37); $Arg^{34}Lys^{36}$-GLP-1(7-37); Val^8Arg^{22}-GLP-1(7-37); Met^8Arg^{22}-GLP-1(7-37);Gly^8His^{22}-GLP-1(7-37); Val^8His^{22}-GLP-

1(7-37); Met^{8}His^{22}-GLP-1(7-37);His^{37}-GLP-1(7-37); Gly^{8}-GLP-1(7-37); Val^{8}-GLP-1(7-37); Met^{8}-GLP-1(7-37);Gly^{8}Asp^{22}-GLP-1(7-37); Val^{8}Asp^{22}-GLP-1(7-37); Met^{8}Asp^{22}-GLP-1(7-37);Gly^{8}Glu^{22}-GLP-1(7-37); Val^{8}Glu^{22}-GLP-1(7-37); Met^{8}Glu^{22}-GLP-1(7-37); Gly^{8}Lys^{22}-GLP-1(7-37); Val^{8}Lys^{22}-GLP-1(7-37); Met^{8}Lys^{22}-GLP-1(7-37); Gly^{8}Arg^{22}-GLP-1(7-37); Val^{8}Lys^{22}His^{37}-GLP-1(7-37); Gly^{8}Glu^{22}His^{37}-GLP-1(7-37); Val^{8}Glu^{22}His^{37}-GLP-1(7-37); Met^{8}Glu^{22}His^{37}-GLP-1(7-37);Gly^{8}Lys^{22} His^{37}-GLP-1(7-37); Met^{8}Lys^{22}His^{37}-GLP-1(7-37);Gly^{8}Arg^{22}His^{37}-GLP-1(7-37); Val^{8}Arg^{22}His^{37}-GLP-1(7-37); Met^{8}Arg^{22}His^{37}-GLP-1(7-37); Gly^{8}His^{22}His^{37}-GLP-1(7-37); Val^{8}His^{22}His^{37}-GLP-1(7-37); Met^{8}His^{22}His^{37}-GLP-1(7-37); Gly^{8}His^{37}-GLP-1(7-37); Val^{8}His^{37}-GLP-1(7-37); Met^{8}His^{37}-GLP-1(7-37);Gly^{8}Asp^{22} His^{37}-GLP-1(7-37); Val^{8}Asp^{22}His^{37}-GLP-1(7-37); Met^{8}Asp^{22}His^{37}-GLP-1(7-37); Arg^{26}-GLP-1(7-36)-amide; Arg^{34}-GLP-1(7-36)-amide; Lys^{36}-GLP-1(7-36)-amide; Arg^{26,34}Lys^{36}-GLP-1(7-36)-amide; Arg^{26,34}-GLP-1(7-36)-amide; Arg^{26,34}Lys^{40}-GLP-1(7-36)-amide; Arg^{26}Lys^{36}-GLP-1(7-36)-amide; Arg^{34}Lys^{36}-GLP-1(7-36)-amide; Gly^{8}-GLP-1(7-36)-amide; Val^{8}-GLP-1(7-36)-amide; Met^{8}-GLP-1(7-36)-amide;Gly^{8}Asp^{22}-GLP-1(7-36)-amide; Gly^{8}Glu^{22}His^{37}-GLP-1(7-36)-amide; Val^{8}Asp^{22}-GLP-1(7-36)-amide; Met^{8}Asp^{22}-GLP-1(7-36)-amide;Gly^{8}Glu^{22}-GLP-1(7-36)-amide; Val^{8}Glu^{22}-GLP-1(7-36)-amide; Met^{8}Glu^{22}-GLP-1(7-36)-amide; Gly^{8}Lys^{22}-GLP-1(7-36)-amide; Val^{8}Lys^{22}-GLP-1(7-36)-amide; Met^{8}Lys^{22}-GLP-1(7-36)-amide; Gly^{8}His^{22}His^{37}-GLP-1(7-36)-amide; Gly^{8}Arg^{22}-GLP-1(7-36)-amide; Val^{8}Arg^{22}-GLP-1(7-36)-amide; Met^{8}Arg^{22}-GLP-1(7-36)-amide;Gly^{8}His^{22}-GLP-1(7-36)-amide; Val^{8}His^{22}-GLP-1(7-36)-amide; Met^{8}His^{22}-GLP-1(7-36)-amide;His^{37}-GLP-1(7-36)-amide; Val^{8}Arg^{22}His^{37}-GLP-1(7-36)-amide; Met^{8}Arg^{22}His^{37}-GLP-1(7-36)-amide; Gly^{8}His^{37}-GLP-1(7-36)-amide; Val^{8}His^{37}-GLP-1(7-36)-amide; Met^{8}His^{37}-GLP-1(7-36)-amide;Gly^{8}Asp^{22} His^{37}-GLP-1(7-36)-amide; Val^{8}Asp^{22}His^{37}-GLP-1(7-36)-amide; Met^{8}Asp^{22}His^{37}-GLP-1(7-36)-amide; Val^{8}Glu^{22}His^{37}-GLP-1(7-36)-amide; Met^{8}Glu^{22}His^{37}-GLP-1(7-36)-amide;Gly^{8}Lys^{22} His^{37}-GLP-1(7-36)-amide; Val^{8}Lys^{22}His^{37}-GLP-1(7-36)-amide; Met^{8}Lys^{22}His^{37}-GLP-1(7-36)-amide;Gly^{8}Arg^{22}His^{37}-GLP-1(7-36)-amide; Val^{8}His^{22}His^{37}-GLP-1(7-36)-amide; Met^{8}His^{22}His^{37}-GLP-1(7-36)-amide; and derivatives thereof.

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Val^{8}Trp^{19}Glu^{22}-GLP-1(7-37), Val^{8}Glu^{22}Val^{25}-GLP-1(7-37), Val^{8}Tyr^{16}Glu^{22}-GLP-1(7-37), Val^{8}Trp^{16}Glu^{22}-GLP-1(7-37), Val^{8}Leu^{16}Glu^{22}-GLP-1(7-37), Val^{8}Tyr^{18}Glu^{22}-GLP-1(7-37), Val^{8}Glu^{22}His^{37}-GLP-1(7-37), Val^{8}Glu^{22}Ile^{33}-GLP-1(7-37), Val^{8}Trp^{16}Glu^{22}Val^{25}Ile^{33}-GLP-1(7-37), Val^{8}Trp^{16}Glu^{22}Ile^{33}-GLP-1(7-37), Val^{8}Glu^{22}Val^{25}Ile^{33}-GLP-1(7-37), Val^{8}Trp^{16}Glu^{22}Val^{25}-GLP-1(7-37), analogues thereof and derivatives of any of these.

In yet another embodiment the GLP-1 agonist is exendin-4 or exendin-3, an exendin-4 or exendin-3 analogue or a derivative of any of these.

Examples of exendins as well as analogues, derivatives, and fragments thereof to be included within the present invention are those disclosed in WO 97/46584, US 5,424,286 and

WO 01/04156. US 5,424,286 describes a method for stimulating insulin release with an exendin polypeptide. The exendin polypeptides disclosed include HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGX; wherein X = P or Y, and HX1X2GTFITSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS; wherein X1X2 = SD (exendin-3) or GE (exendin-4)). WO 97/46584 describes truncated versions of exendin peptide(s). The disclosed peptides increase secretion and biosynthesis of insulin, but reduce those of glucagon. WO 01/04156 describes exendin-4 analogues and derivatives as well as the preparation of these molecules. Exendin-4 analogues stabilized by fusion to serum albumin or Fc portion of an Ig are disclosed in WO 02/46227.

In one embodiment, the exendin-4 analogue is HGEGTFTSDLSKQMEEEAVRL-FIEWLKNGGPSSGAPPSKKKKKK-amide.

Where the peptide to be included in the formulation of the invention is a GLP-1 agonist, the GLP-1 agonist is present in a concentration from about 0.1 mg/ml to about 100 mg/ml, more preferably in a concentration from about 0.1 mg/ml to about 50 mg/ml, and most preferably in a concentration of from about 0.1 mg/ml to about10 mg/ml.

In another embodiment, the peptide to be included in the formulation of the invention is insulin , where "insulin" is understood to mean human insulin, [where "human insulin" means insulin having the amino acid sequence shown in DSHW Nicol and LF Smith: Nature, (1960) 4736:483-485, which is hereby incorporated by reference], human insulin analogs, human insulin derivatives or mixtures thereof, where examples of insulin analogs and derivatives are those disclosed in EP 0 792 290 (Novo Nordisk A/S), EP 0 214 826 and EP 0 705 275 (Novo Nordisk A/S), US 5,504,188 (Eli Lilly), EP 0 368 187 (Aventis), US patents 5,750,497 and 6,011,007, EP 375437 and EP 383472 and where such insulins may include, but are not limited to, NPH insulin, Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin, Lys^{B29}-(N^{ε}-(γ-glutamyl-N^{α}-lithocholyl) des(B30) human insulin, $N^{\alpha B29}$-octanoyl insulin, 30/70 mixtures of prompt insulin zinc (SemiLente®) with extended insulin zinc (Ultralente®), sold commercially as Lente®, insulin glargine (Lantus®) or extended insulin zinc (Ultralente®), Lys^{B28} Pro^{B29} human insulin (Humalog®) , Asp^{B28} human insulin, insulin aspart (Novolog®), or a 30/70 mixture of insulin aspart and insulin aspart protamine (NovoMix®) .

In one embodiment, the insulin is a derivative of human insulin or a human insulin analogue where the derivative contains at least one lysine residue and a lipophilic substituent is attached to the epsilon amino group of the lysine residue.

In one embodiment, the lysine residue to which the lipophilic substituent is attached is present at position B28 of the insulin peptide.

In an alternative embodiment, the lysine residue to which the lipophilic substituent is attached is present at position B29 of the insulin peptide.

In yet another embodiment, lipophilic substituent is an acyl group corresponding to a carboxylic acid having at least 6 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group, branched or unbranched, which corresponds to a carboxylic acid having a chain of carbon atoms 8 to 24 atoms long.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a fatty acid having at least 6 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 6 to 24 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 8 to 12 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 10 to 16 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an oligo oxyethylene group comprising up to 10, preferably up to 5, oxyethylene units.

In another preferred embodiment, the lipophilic substituent is an oligo oxypropylene group comprising up to 10, preferably up to 5, oxypropylene units.

In one preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys; Phe^{B1} may be deleted; the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms; and 2-4 Zn^{2+} ions may be bound to each insulin hexamer with the proviso that when B30 is Thr or Ala and A21 and B3 are both Asn, and Phe^{B1} is not deleted, then 2-4 Zn^{2+} ions are bound to each hexamer of the insulin derivative.

In another preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys, with the proviso that if the B30 amino acid residue is Ala or Thr, then at least one of the residues A21 and B3 is different from Asn; Phe^{B1} may be deleted; and the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms.

In another preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys; Phe^{B1} may be deleted; the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms; and 2-4 Zn^{2+} ions are bound to each insulin hexamer.

Where the peptide to be included in the formulation of the invention is an insulin, the insulin is present in a concentration from about 0.5 mg/ml to about 20 mg/ml, more preferably in a concentration from about 1 mg/ml to about 15 mg/ml.

In another embodiment, the peptide to be included in the formulations of the invention is hGH or Met-hGH.

Where the peptide to be included in the formulation of the invention is hGH or Met-hGH, the hGH or Met-hGH is present in a concentration from about 0.5 mg/ml to about 50 mg/ml, more preferably in a concentration from about 1 mg/ml to about 10 mg/ml.

In yet another embodiment, the peptide to be included in the formulations of the invention is GLP-2 or an analogue or derivative thereof.

Where the peptide to be included in the formulation of the invention is GLP-2 or an analogue or derivative thereof, the GLP-2 or an analogue or derivative thereof is present in a concentration from about 1 mg/ml to about 100 mg/ml, more preferably in a concentration from about 1 mg/ml to about 10 mg/ml.

In yet a further embodiment, the peptide to be included in the formulations of the invention is Factor VII or Factor VIIa or an analogue or derivative thereof.

Where the peptide to be included in the formulation of the invention is Factor VII or Factor VIIa or an analogue or derivative thereof, the Factor VII or Factor VIIa or an analogue or derivative thereof is present in a concentration from about 0.1 mg/ml to about 10 mg/ml, more preferably in a concentration from about 0.5 mg/ml to about 5 mg/ml.

In one embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 1 to about 50 mg/ml.

In another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 5 to about 25 mg/ml.

In yet another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 8 to about 16 mg/ml.

In yet a further embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 13 to about 15 mg/ml.

In still another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 13.5 to about 14.5 mg/ml.

In another embodiment of the invention, the formulation has a pH in the range from about 7.0 to about 9.5 where the term "about" as used in connection with pH means + or – 0.1 pH units from the stated number.

In a further embodiment of the invention, the formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the formulation has a pH in the range from about 7.2 to about 8.0.

In a preferred embodiment of the invention, the formulations contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

Where a buffer is to be included in the formulations of the invention, the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, or mixtures thereof. Each one of these specific buffers constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the buffer is glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate or mixtures thereof.

Where a pharmaceutically acceptable preservative is to be included in the formulations of the invention, the preservative is selected from the group consisting of phenol, m-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, or mixtures thereof. Each one of these specific preservatives constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the preservative is phenol or m-cresol.

In a further embodiment of the invention the preservative is present in a concentration from about 0.1 mg/ml to about 50 mg/ml, more preferably in a concentration from about 0.1 mg/ml to about 25 mg/ml, and most preferably in a concentration from about 0.1 mg/ml to about 10 mg/ml

The use of a preservative in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further embodiment of the invention the formulation may further comprise a chelating agent where the chelating agent may be selected from salts of ethlenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof.

Each one of these specific chelating agents constitutes an alternative embodiment of the invention.

In a further embodiment of the invention the chelating agent is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 0.1mg/ml to 2mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 2mg/ml to 5mg/ml.

The use of a chelating agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further embodiment of the invention the formulation may further comprise a stabiliser selected from the group of high molecular weight polymers or low molecular compounds where such stabilizers include, but are not limited to, polyethylene glycol (e.g. PEG 3350), polyvinylalcohol (PVA), polyvinylpyrrolidone, carboxymethylcellulose, different salts (e.g. sodium chloride), L-glycine, L-histidine, imidazole, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and mixtures thereof. Each one of these specific stabilizers constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the stabiliser is selected from the group consisting of L-histidine, imidazole and arginine.

In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1mg/ml to 50mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 5mg/ml to 10mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0mg/ml to 20mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 20mg/ml to 30mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 30mg/ml to 50mg/ml.

In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1mg/ml to 50mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 5mg/ml to 10mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 10mg/ml to 20mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentra-

tion from 20mg/ml to 30mg/ml. In a further embodiment of the invention the low-molecular weight compound is present in a concentration from 30mg/ml to 50mg/ml.

The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further embodiment of the invention the formulation of the invention may further comprise a surfactant where a surfactant may be selected from a detergent, ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, such as 188 and 407, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives such as alkylated and alkoxylated derivatives (tweens, e.g. Tween-20, or Tween-80), monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, glycerol, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids, glycerophospholipids (lecithins, kephalins, phosphatidyl serine), glyceroglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, docusate calcium, docusate potassium, SDS (sodium dodecyl sulfate or sodium lauryl sulfate), dipalmitoyl phosphatidic acid, sodium caprylate, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (e.g. 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, zwitterionic surfactants (e.g. N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (e.g. cetyl-trimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl β-D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35), fusidic acid derivatives- (e.g. sodium tauro-dihydrofusidate etc.), long-chain fatty acids and salts thereof C6-C12 (eg. oleic acid and caprylic acid), acylcarnitines and derivatives, N^{α}-acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of

lysine or arginine, N^{α}-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N^{α}-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof. Each one of these specific surfactants constitutes an alternative embodiment of the invention.

The use of a surfactant in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

The formulations of the invention may be prepared by conventional techniques, *e.g.* as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product..

As mentioned above, in a preferred embodiment, the formulations of the invention contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

In one embodiment, the method for preparing such a peptide formulation comprises:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;
b) preparing a second solution by dissolving the peptide in water;
c) mixing the first and second solutions; and
d) adjusting the pH of the mixture in c) to the desired pH.

In another embodiment, the method for preparing such a peptide formulation comprises:

a) preparing a first solution by dissolving preservative and buffer in water;
b) adding propylene glycol to the first solution;
c) mixing the first solution with a second solution containing peptide dissolved in water; and
d) adjusting the pH of the mixture in c) to the desired pH.

In yet another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a solution by dissolving preservative, buffer and propylene glycol in water;
b) adding the peptide to the solution of step a); and
c) adjusting the pH of the solution of step b) to the desired pH.

As the formulations of the invention are optimal for production and for use in injection devices since they exhibit reduced deposits of production equipment and reduced clogging of injection devices, the above methods of production can be used to produce peptide formulations suitable for use in production and/or for use in injection devices.

The formulations of the invention are suitable for administration to a mammal, preferably a human. The route of administration of the formulations of the invention may be any route which effectively transports the peptide contained in the formulation to the appropriate or desired site of action, such as oral, nasal, buccal, pulmonal, transdermal or parenteral.

Due to the ability of propylene glycol to reduce clogging of injection devices when compared to other isotonic agents and to mannitol in particular, in a preferred embodiment, the formulations of the invention are to be administered parenterally to a patient in need thereof. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump.

A further option is a composition which may be a powder or a liquid for the administration of the formulation in the form of a nasal or pulmonal spray. As a still further option, the formulation can also be administered transdermally, *e.g.* from a patch, optionally a iontophoretic patch, or transmucosally, *e.g.* bucally. The above-mentioned possible ways to administer the formulations of the invention are not to be considered as limiting the scope of the invention.

Of course, it is understood that depending on the peptide or peptides included in the formulations of the invention, the formulations may be used in methods of treatment of diseases or conditions for which use of the peptide is indicated. One skilled in the art would understand that when used in such methods of treatment, the formulations would have to be administered in amount effective to treat the condition or disease for which the peptide was being administered where an "effective amount" or an "amount...effective" is understood to mean a dosage which is sufficient in order for the treatment of the patient with the disease or condition to be treated to be effective compared to treatment without the administered dosage. It is to be understood that "an effective amount" is the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, the condition or disease to be treated (e.g. diabetes, obesity, weight loss, gastric ulcers), patient-related factors (e.g. weight, health, age, etc.), presence of co-administered medications (e.g. insulin), time of administration, or other factors known to a medical practitioner.

The present invention also relates to a method for reducing deposits on production equipment during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment as described in the Examples.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

The present invention also relates to a method for reducing deposits in the final product during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

The present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study as described in the Examples.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

All scientific publications and patents cited herein are specifically incorporated by reference. The following examples illustrate various aspects of the invention but are in no way intended to limit the scope thereof.

EXAMPLES

EXAMPLE 1

Simulated filling experiments, drop and clogging tests of replacement candidates for mannitol

As laboratory experiments have shown that with regards to clogging of needles and deposits on needles, formulations without peptide ("placebo") give the same conclusions as formulations with peptide at 0.3-5.0 mg/ml, the screening studies in Example 1 have been done using placebo except where indicated otherwise.

Preparation Of Formulations With Different Isotonic Agents

Preservative (5.5 mg/ml phenol) and buffer 1.24 mg/ml disodium hydrogen phosphate, dihydrate) were dissolved in water and the isotonic agent was added while stirring. pH was adjusted to pH 7.9 using Sodium Hydroxide and/or Hydrochloric acid. Finally, the formulation was filtered through a 0.22 µm filter. The isotonic agents tested in each formulation and their concntrations are shown in Table 1.

Table 1 Composition of the tested formulations

Formulation no.	Tonicity modifier
1	Glucose monohydrate (38.0 mg/ml)
2	Laktose monohydrate (65.0 mg/ml)
3	Maltose (67.2 mg/ml)
4	Glycine (15.1 mg/ml)
5	Polyethylenglycol 400 (77.5 mg/ml)
6	L-arginin (24.6 mg/ml)
7	Myo-Inositol (35.2 mg/ml)
8	Propylene glycol (13.7 mg/ml)
9	Dimethylsulfon (18 mg/ml)
10	Mannitol (35.9 mg/ml)
11	Sorbitol (39.5 mg/ml)
12	Xylitol (39.5 mg/ml)
13	Sucrose (79.1 mg/ml
14	Glycerol (16 mg/ml)

Osmolarity

The osmolarity of the different placebo formulations was determined and the results are shown in Table 2.

An isotonic solution has an osmolarity of around 0.286 osmol/L. As can be seen from Table 2 three of the formulations (PEG 400, sucrose and xylitol) are more than 20% from being isotonic (0.229-0.343 osmol/l), however for these kind of experiments the osmolarity is not expected to influence the results, though, the tonicity of the formulations should be adjusted in future experiments.

Table 2. The measured osmolarity of the formulations

Formulation no.	Isotonic agent	Osmolarity
1	Glucose monohydrate (38.0 mg/ml)	0.315
2	Laktose monohydrate (65.0 mg/ml)	0.283
3	Maltose (67.2 mg/ml)	0.306
4	Glycine (15.1 mg/ml)	0.286
5	Polyethylenglykol 400 (77.5 mg/ml)	0.370
6	L-arginin(24.6 mg/ml)	0.318
7	Myo-Inositol (35.2 mg/ml)	0.285
8	Propylene glycol (13.7 mg/ml)	0.268
9	Dimethylsulfon (18 mg/ml)	0.274
10	Mannitol (35.9 mg/ml)	0.284
11	Sorbitol (39.5 mg/ml)	0.310
12	Xylitol (39.5 mg/ml)	0.351
13	Sucrose (79.1 mg/ml	0.346
14	Glycerol (16 mg/ml)	0.262

Drop test

A droplet of each formulation is placed on a microscope slide and let to dry. The deposit is visually examined by eye and light microscope.

A photograph of the dried droplets of some of the formulations is shown in Figure 1. In this figure it is clearly observed that mannitol cause deposits on the microscope slide when let to dry. The droplet on the far right (Form 1) contains mannitol and Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

In Figure 2, the candidates causing the most deposits on the microscope slide are shown. For comparison glycerol, which does not cause deposits, is shown.

Clogging test

In this test 10 NovoPens® 1.5 ml mounted with NovoFine 30® G (G 30 needle) were tested for each formulation, 5 of them placed in upright and 5 in horizontal position. The Pensystems were stored at room temperature in between testing. Each day the needle was examined for deposits and an air shot was performed prior to injection into a tissue. Degree of resistance and clogging, if any, was noted. Injections were made on a daily basis with the same needle, and this was done for 9 working days for all the formulations.

The results from the clogging test are shown in Table 3.

Table 3 Clogging test in NovoPen 1.5 using 30G NovoFine

Isotonic agent (no. of observations)	Some resistance	Resistance	Much resistance	clogged	Drop at top of needle	Dried drop at needle top	Gel-like drop on needle	Deposits on needle
Mannitol (90)	10	0	0	0	0	2	0	43
Glycerol (90)	13	0	0	0	1	0	3	0
Sucrose (90)	23	0	0	0	0	0	21	0
Propylene glycol (90)	20	0	0	0	0	0	0	0
PEG 400 (90)	25	1	0	0	12 (5 at needle)	0	0	0
arginin (90)	26	2	0	0	3 (2 at needle)	1	0	0
Xylitol (90)	14	0	0	0	5	0	0	0
Dimethyl-sulfon (90)	21	0	0	0	4	0	0	0
sorbitol (90)	12	0	0	0	9	1	0	1
Myo-inositol (90)	20	1	2	6	6	0	0	47
Glucose (90)	32	11	5	0	16 (7 at needle)	1	0	(1 at needle)
glycine (90)	41	9	2	0	1 (2 at needle)	0	0	31 (2 at needle)
maltose (90)	35	8	7	4	16 (6 at needle)	0	0	1 (5 at needle)
laktose (90)	44	10	8	0	5	0	0	31 (2 at needle)

In Table 3 and in Figure 3 it was observed that inositol and maltose clogged the needle. For comparison glycerol is shown in Figure 3. In Figure 4, and in Table 3, it was observed that formulations containing glycine, lactose and mannitol gave rise to a lot of deposits on the needle. For glycine, the deposits were a droplet deposited down the needle, whereas for lactose and mannitol the deposits occurred at the top of the needle.

Simulated filling

1 L of each formulation was subjected to a simulated filling experiment which lasted for 24 hours. After 24 hours the filling equipment was inspected for the presence of deposits.

Based on the results from the simulated filling studies (data not shown), the placebo formulations can be divided into three categories. 1. Those isotonic agents that do not cause deposits on the filling equipment: Xylitol, glycerol, glucose monohydrate, maltose, PEG 400 and propylene glycol. 2. Those isotonic agent that cause few deposits and have superior filling properties compared to mannitol: Sorbitol, sucrose and glycine. 3. Those isotonic agent that are comparable or worse than mannitol: Mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

Conclusion

In the simulated filling experiment xylitol, glycerol, glucose, maltose, PEG 400, propylene glycol, sorbitol, sucrose and glycine were found to be suitable replacements candidates for mannitol. However, as glucose is a reducing saccharide, and therefore is able to initiate unwanted degradation in the formulation, this tonicity modifier is ruled out. Furthermore, maltose is ruled out due to clogging of needles. This leads to the following candidates: glycerol, xylitol, sorbitol, sucrose, glycine, propylene glycol and PEG 400, which are found to have suitable properties as replacements candidates for mannitol in peptide formulations with regards to drop test, clogging of needles and simulated filling.

However, on the basis of the following considerations, propylene glycol was chosen as the isotonic agent over the other candidates to be further investigated in head to head comparison studies with mannitol:

a. propylene glycol was observed to have no influence on the physical and chemical stability of Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations;

b. propylene glycol was observed to have no influence on antimicrobial preservative testing; and

c. use of propylene glycol would no require that further toxicity studies be tested

EXAMPLE 2

Comparison Of Mannitol and Propylene Glycol-Containing Placebo Formulations In Simulated Filling Studies and Simulated Use Studies

Preparation Of Formulations

Preservative and buffer were dissolved in water and the isotonic agent was added while stirring. pH was adjusted to the aimed pH using Sodium Hydroxide and/or Hydrochloric acid. Finally, the formulation was filtered through a 0.22 µm filter. The compositions of the formulations were as follows:

Disodium hydrogen phosphate, dihydrate:	1.42 mg/ml
Phenol:	5.5 mg/ml
Propylene glycol or mannitol:	13.7 or 35.9 mg/ml
Water for Injection:	up to 1.0 ml.
pH: 7.90	

Simulated Filling Study

A simulated filling study lasting 24 hours was performed as described in Example 1 and after 24 hours, the filling equipment was inspected for the presence of deposits. No deposits were observed on the filling equipment for the propylene glycol formulation. By comparison, after 24 hours, a lot of deposits were observed on the filling equipment for the mannitol formulation (see Figure 6).

Simulated In Use Study

For the simulated in use study, a clogging test was conducted as described in Example 1. The same needle was used during the study period of ten working days and each day, the needle was inspected for the presence of deposits. Figure 7 shows photographs of needles dosed with the propylene glycol (left-hand panel) or mannitol (right-hand panel) containing formulations. Deposits on the needle were observed in 48% of the cases when mannitol was used as an isotonic agent whereas no deposits were observed when propylene glycol was used as the isotonic agent.

Example 3

Comparison of Propylene Glycol to Mannitol In Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) Containing Formulations

Preparation of Formulations

Preservative, isotonic agent (mannitol or propylene glycol) and buffer were dissolved in water and pH was adjusted to the desired pH. Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) was dissolved in water while stirring slowly. The two solutions were then mixed and pH adjusted to the desired pH using sodium hydroxide and/or hydrochloric acid. Finally, the formulation was filtered through a 0.22 µm filter. The compositions of the formulations were as follows:

Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) (6.25 mg/ml),
Disodium hydrogen phosphate, dihydrate (1.42 mg/ml),
Phenol (5.5 mg/ml),
mannitol or propylene glycol (35.9 or 14.0 mg/ml),
Water for Injection (up to 1.0 ml),
pH: 8.15

Simulated In Use Study

For the simulated in use study, a clogging test was conducted as described in Example 1 except that a G31 needle was used. The same G31 needle was used during the study period of ten working days and each day, the needle was inspected for the presence of deposits. Figure 8 shows photographs of needles dosed with the propylene glycol (bottom panel) or mannitol (top panel) containing formulations.

For the mannitol containing formulation, clogging of the needle was observed in 1 out of 10 cases on day 4, 2 out of 10 cases on day 5, 3 out of 10 cases on day 8 and 4 out of 10 cases on day 9. By comparison, no clogging of needles was observed for the propylene glycol containing formulation.

It is believed that similar results to those obtained with the above-described propylene glycol-containing formulation would also be obtained if the pH was adjusted to 7.40, 7.70 or 7.90. In addition, additional formulations which could be tested include those having the following compositions:

Buffering agents: glycylglycine (1.32 mg/ml), L-Histidine (1.55 mg/ml), Hepes (2.38 mg/ml), or bicine (1.63 mg/ml)

Preservatives: phenol (5.0 or 5.5 mg/ml), benzylalcohol (18 mg/ml) or a mixture of m-cresol and phenol (2.5/2.0 mg/ml)

Propylene glycol: 14.0 or 14.3 mg.ml

Water for injection: up to 1.0 ml
pH: 7.40, 7.70, 7.90 or 8.15

Example 4

Influence of Peptide Concentration On Clogging of Needles

Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) formulations were prepared as described in Example 3 using peptide concentrations ranging from 0-5 mg/ml of Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37). The compositions of the formulations were as follows:
Liraglutide: 0, 0.3, 3 and 5 mg/ml
Disodium hydrogen phosphate, dihydrate: 0.71 mg/ml
Sodium dihydrogenphosphate, dihydrate: 0.62 mg/ml
Mannitol: 36.9 mg/ml
Phenol: 5.0 mg/ml
Water for injection: up to 1.0 ml
pH 7.40

A simulated in use study was conducted as in Example 3 except that a G30 needle was used and the results (data not shown) indicated that the clogging effect of the mannitol-containing formulations relative to the absence of clogging with the propylene glycol formulations was observed independent of the peptide concentration.

Example 5

Clogging of needles in Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations Containing Mannitol

Preparation Of Formulations

The Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin-containing formulation was prepared as follows:

a) Prepared a first solution by dissolving buffer, sodium chloride, preservatives (phenol and m-cresol) and mannitol in water

b) Prepared a second solution of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and zinc acetate dissolved in water

c) added the peptide-containing solution of step b) to the solution of step a); and

d) adjusted the pH of the solution to the desired pH

The composition of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin-containing formulation prepared in the above manner was as follows:

Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin (2400 nmol), Phenol (1.80 mg/ml), m-cresol (2.06 mg/ml), Mannitol (30.0 mg/ml), disodiumphosphate, dihydrate (0.890 mg/ml), Sodium chloride (1.17 mg/ml), Zinc acetate (65.4 ug/ml), water for injection (up to 1.0 ml), pH: 7.4

The NovoMix 30-containing formulation was prepared as follows:

a) Prepared a solution by dissolving buffer, sodium chloride, phenol, mannitol and sodium hydroxide in water

b) Prepared a solution of sodium chloride, phenol and mannitol in water

c) Prepared a solution of protamine sulphate in water

d) Prepared a solution of insulin, hydrochloric acid and zinc in water

e) Solutions b), c) and d) were mixed

f) Solution e) was added to the solution of step a)

g) Adjustedthe pH of the solution to the desired pH and crystallized at room temperature

h) Prepared a solution by dissolving m-cresol, phenol and mannitol in water

i) Solution h) is added to the crystalline fraction of step g); and

j) Adjusted the pH to the desired pH

The composition of the NovoMix 30-containing formulation prepared in the above manner was as follows:

Insulin aspart (100 units/ml), protamine sulphate (approx. 0.33 mg/ml), phenol (1.50 mg/ml), m-cresol (1.72 mg/ml), mannitol (30.0 mg/ml), disodiumphosphate dihydrate (1.25 mg/ml), sodium chloride (0.58 mg/ml), zinc (19.6 ug/ml), water for injection (up to 1.0 ml), pH: 7.3.

Results

A simulated in use study was conducted as described in Example 3 using G31 needles where 20 needles were investigated for 10 days. The results were as follows: Clogging of needles was observed for Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin on day 2 (5%), day 3 (70%) and on day 4 (100%). Clogging of needles for NovoMix 30 was observed on day 3 (5%), day 4 (10%), day 5 (35%), day 6 (40%), day 8 (50%), day 9 (55%) and day 10 (80%). Thus, the effect of mannitol on the clogging of needles is independent of the type of peptide included in the formulations since a comparable clogging effect was observed with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37), Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30.

Example 6

Testing of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations containing propylene glycol

The preparation and composition of the Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations will be as described in Example 5 except that mannitol will be replaced with a concentration of propylene glycol that assures tonicity. A simulated in use test will then be conducted as described in Example 5.

Based on the fact that the clogging effect of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 mannitol-containing formulations was similar to that observed with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) mannitol-containing formulations, it is believed that the effect of propylene glycol on the clogging effect of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30-containing formulations will be similar to that observed with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations.

Claims

1. A pharmaceutical formulation comprising at least one peptide and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.

2. The formulation according to claim 1, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

3. The formulation according to claim 1, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

4. The formulation according to claim 1, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

5. The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 9.5.

6. The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.0.

7. The formulation according to claim 1, wherein the pH of said formulation is about 7.2 to about 8.0.

8. The formulation according to claim 1, further comprising a preservative.

9. The formulation according to claim 8, wherein said preservative is present in a concentration from 0.1mg/ml to 20mg/ml.

10. The formulation according to claim 1, further comprising a buffer.

11. The formulation according to claim 10, wherein said buffer is selected from the group consisting of glycylglycine, L-histidine, Hepes, bicine and disodium phosphate dihydrate.

12. The formulation according to claim 1, wherein said peptide is a GLP-1 agonist.

13. The formulation according to claim 12, wherein said GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

14. The formulation according to claim 13, wherein said GLP-1 agonist is a derivative of GLP-1(7-36) or GLP-1(7-37) or a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, where said derivative has a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine.

15. The formulation according to claim 14, wherein said lipophilic substituent has from 8 to 40 carbon atoms.

16. The formulation according to claim 15, wherein said spacer is an amino acid.

17. The formulation according to claim 16, wherein said GLP-1 agonist is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

18. The formulation according to claim 12, wherein said GLP-1 agonist is selected from the group consisting of Gly^{8}-GLP-1(7-36)-amide, Gly^{8}-GLP-1(7-37), Val^{8}-GLP-1(7-36)-amide, Val^{8}-GLP-1(7-37), $Val^{8}Asp^{22}$-GLP-1(7-36)-amide, $Val^{8}Asp^{22}$-GLP-1(7-37) , $Val^{8}Glu^{22}$-GLP-1(7-36)-amide , $Val^{8}Glu^{22}$-GLP-1(7-37), $Val^{8}Lys^{22}$-GLP-1(7-36)-amide, $Val^{8}Lys^{22}$-GLP-1(7-37), $Val^{8}Arg^{22}$-GLP-1(7-36)-amide, $Val^{8}Arg^{22}$-GLP-1(7-37), $Val^{8}His^{22}$-GLP-1(7-36)-amide, $Val^{8}His^{22}$-GLP-1(7-37), Arg34GLP-1(7-37); Arg26,34,Lys36GLP-1(7-36); Arg26GLP-1(7-37); and Gly8,Arg26,34,Glu37,Lys38GLP-1(7-38) analogues thereof and derivatives of any of these.

19. The formulation according to claim 1, wherein said peptide is selected from insulin, an insulin analogue, a derivative of insulin or an insulin analogue or a mixture of any of the foregoing.

20. The formulation according to claim 19, wherein said peptide is an insulin derivative in which said derivative contains a lysine residue to which a lipophilic substituent of at least six carbon atoms is attached.

21. The formulation according to claim 20, wherein the insulin derivative is Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin.

22. The formulation according to claim 20, wherein said insulin derivative is $N^{\alpha B29}$-octanoyl insulin.

23. The formulation according to claim 19, wherein said peptide is a 30/70 mixture of insulin aspart and insulin aspart protamine.

24. The formulation according to claim 1, wherein said peptide is human growth hormone (hGH) or Met-hGH.

25. The formulation according to claim 24, wherein said peptide is exendin 4, an exendin 4 analogue or a derivative of exendin 4 or an exendin 4 analogue.

26. The formulation according to claim 25, wherein said peptide is exendin 4.

27. The formulation according to claim 25, wherein said peptide is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPSKKKKKK-amide.

28. A method of preparing a peptide formulation suitable for use in an injection device, said method comprising preparing a formulation containing peptide and propylene glycol and optionally a buffer and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from about 7.0 to about 10.0.

29. The method according to claim 28, wherein said peptide, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;
b) preparing a second solution by dissolving the peptide in water;
c) mixing the first and second solutions; and
d) adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

30. The method according to claim 28, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

31. The method according to claim 28, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

32. The method according to claim 28, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

33. The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 9.5.

34. The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 8.0.

35. The method according to claim 28, wherein the pH of said formulation is about 7.2 to about 8.0.

36. A method for reducing deposits on production equipment during production of a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

37. The method according to claim 36, wherein the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

38. The method according to claim 36, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

39. A method for reducing deposits in the final product during production of a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

40. The method according to claim 39, wherein the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials

and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

41. The method according to claim 39. wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

42. A method for reducing the clogging of injection devices by a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

43. The method according to claim 42, wherein the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

44. The method according to claim 42, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

Abstract

The present invention relates to pharmaceutical formulations comprising a peptide and propylene glycol, to methods of preparing such formulations, and to uses of such formulations in the treatment of diseases and conditions for which use of the peptide contained in such formulations is indicated. The present invention further relates to methods for reducing the clogging of injection devices by a peptide formulation and for reducing deposits on production equipment during production of a peptide formulation.

FIGURE 1

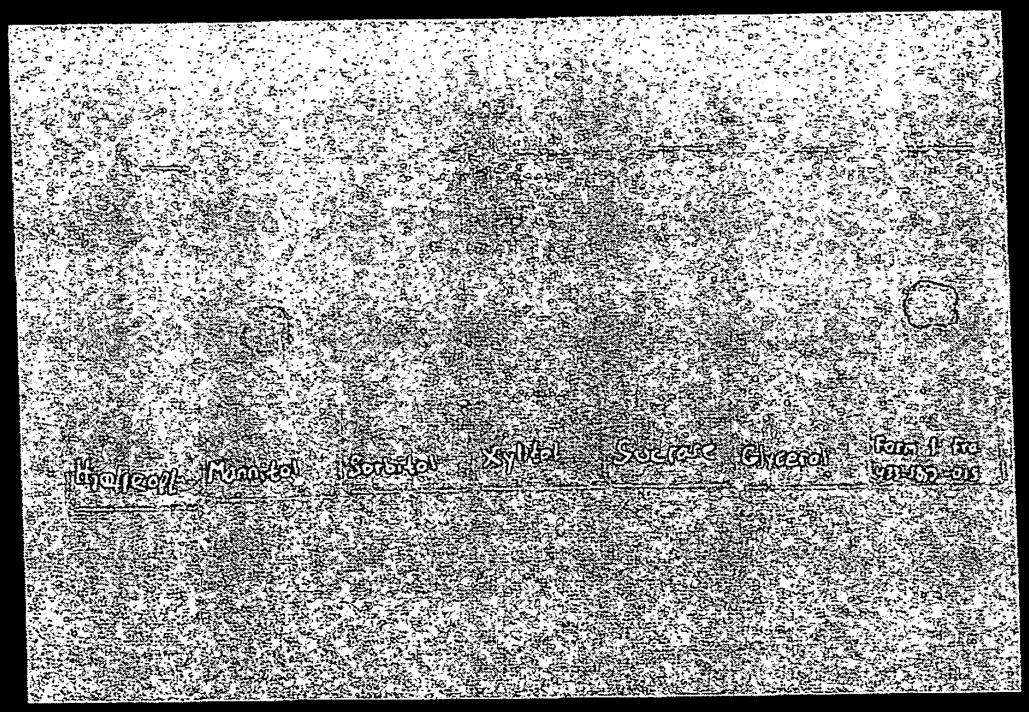


FIGURE 2

FIGURE 3

FIGURE 4

FIGURE 5

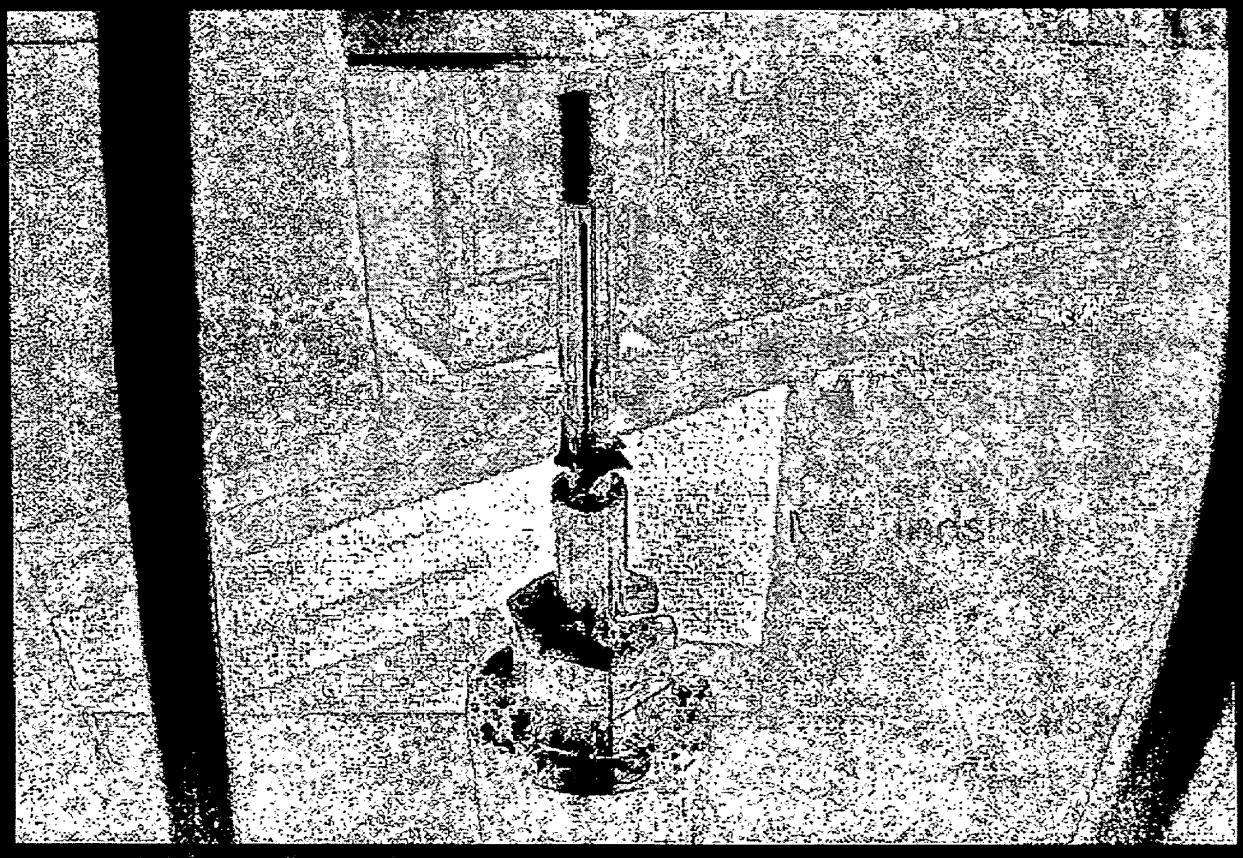


FIGURE 6

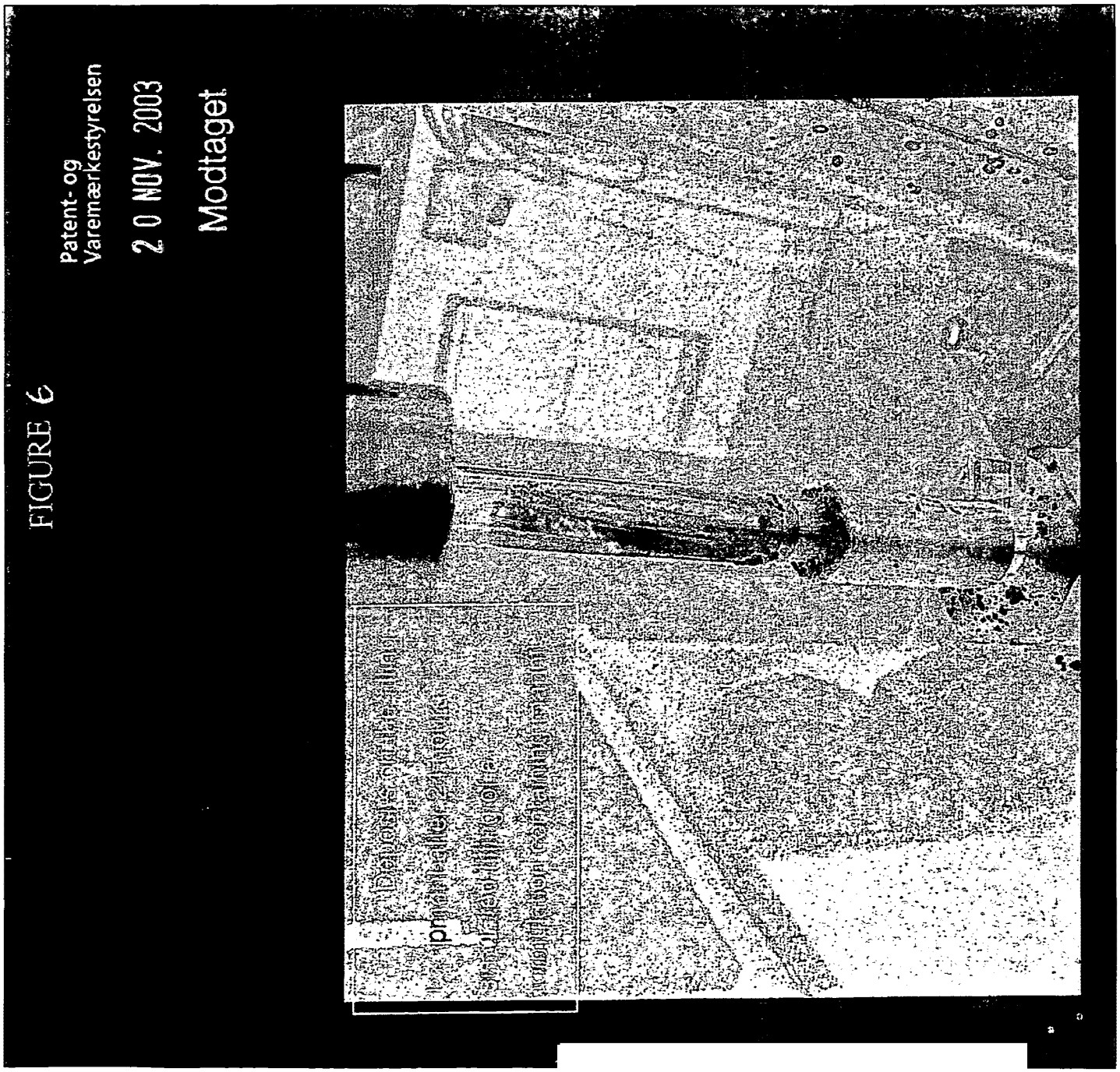


FIGURE 7

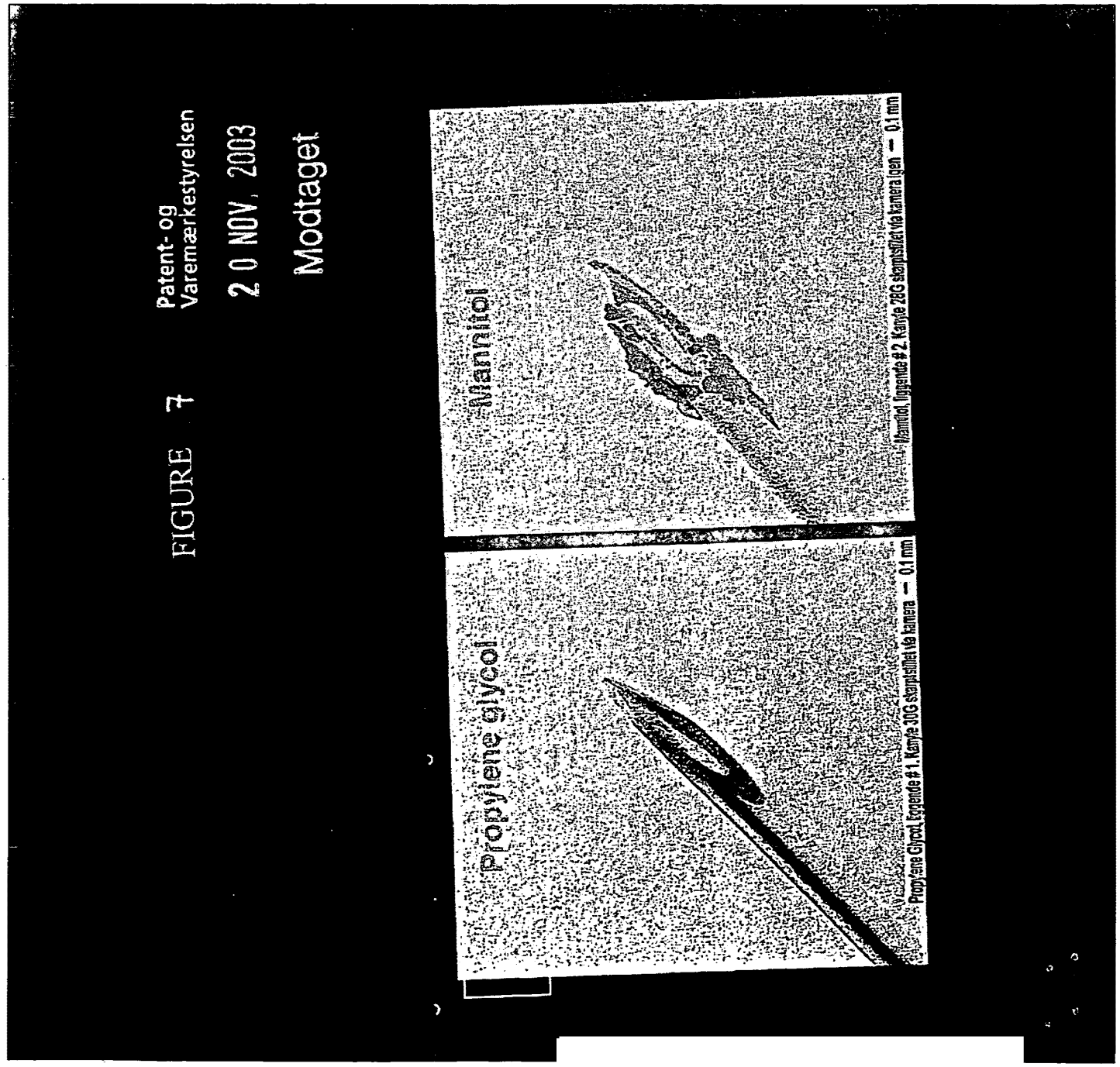
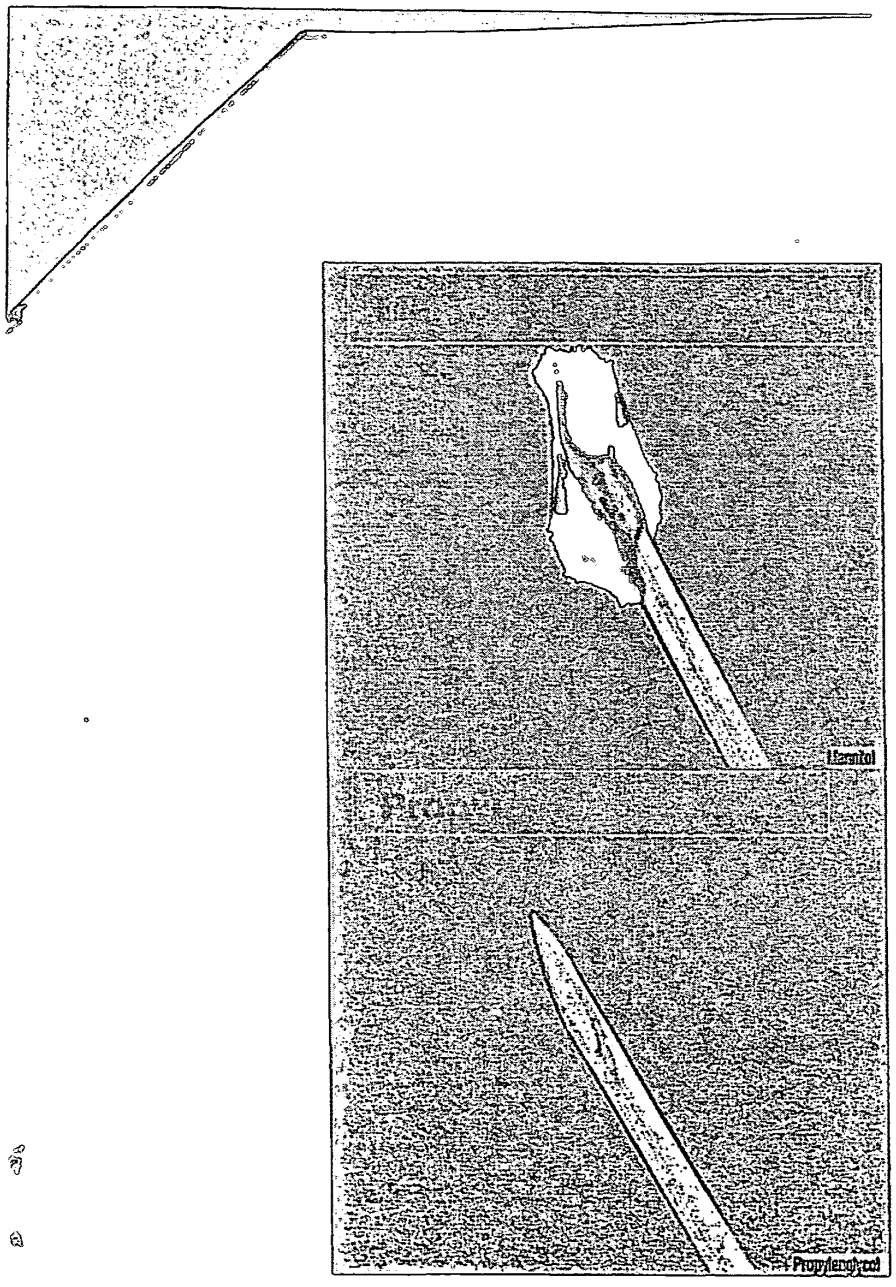


FIGURE 8



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

23650 7590 06/16/2008

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

NOTIFICATION DATE	DELIVERY MODE
06/16/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
KSHL@novonordisk.com
KISW@novonordisk.com

Office Action Summary	Application No.	Applicant(s)	
	11/435,977	PEDERSEN ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-44* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 12-18, drawn to formulations of GLP-1 and analogues, classified in class 514, subclass 2.

   II. Claims 19-23, drawn to formulations of insulins and its analogues, classified in class 514, subclass 3.

   III. Claim 24, drawn to formulations of human growth factor, classified in class 514, subclass 2.

   IV. Claims 25-27, drawn to formulations of exendin-4 and its analogues, classified in class 514, subclass 2.

   V. Claims 28-44, drawn to a method of preparing peptide formulations for an injectable device, classified in class 514, subclass 2.

2. Claims 1-11 link(s) inventions I-IV. The restriction requirement among the linked inventions is **subject to** the nonallowance of the linking claim(s), claims 1-11. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are

governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

3. The inventions are distinct, each from the other because of the following reasons:

Inventions I-IV are directed to related peptides. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed peptides have materially different chemical structures and biological functions. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Inventions I-IV are related to invention V as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that

product. See MPEP § 806.05(h). In the instant case the claimed products could be used in a materially different process such as a method of treating a disease.

4. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an

election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

5. This application contains claims directed to the following patentably distinct species of GLP-1 peptides: GLP-1(7-36)-amide, GLP-1(7-37), Gly8-GLP-1(7-36)-amide, Arg34, Lys26(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP- 1 (7-37), GlyS-GLP-1(7-37), VaP-GLP-1(7-36)-amide, ValS-GLP-1 (7-37), Va18Asp22-GLP-1 (7-36)-amide, ValSAsp22-GLP-1 (7-37), ValSGlu22-GLP-1 (7-36)-amide, ValaGlu22-GLP-1(7-37), Va18Lys22-GLP-1 (7-36)-amide, Va18Lys22-GLP-1 (7- 37), ValSArg22-GLP-1(7-36)-amide, ValBArg22-GLP-1 (7-37), ValBHis22-GLP-1 (7-36)-amide, ValSHis22-GLP-1(7-37), Arg34GLP-1(7-37); Arg26,34,Lys36GLP-1(7-36); Arg26GLP-1(7-37); and Gly8,Arg26,34,Glu37,Lys38GLP-1(7-38). The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

If Group I or V are elected, Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 12-16 and 18 are generic.

6. This application contains claims directed to the following patentably distinct species of insulin peptides: Lysβ29 (Nε-tetradecanoyl)des(B30) human insulin and $N^{L\beta 29}$-octanoyl insulin. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

If Group II or V are elected, Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 19, 20 and 23 are generic.

7. This application contains claims directed to the following patentably distinct species of exendin-4 peptides: exendin-4 and SEQ ID NO: 1. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

If Group IV or V are elected, Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 25 is generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search

queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

9. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder

in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday, 9:00 A.M. to 3:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

RESPONSE TO RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This paper is being filed in response to the Office Action mailed June 16, 2008 that made restriction and election of species requirements. Applicants were requested to elect one of five (5) designated groups.

I. Claims 12-18, drawn to formulations of GLP-1 and analogues, classified in class 514, subclass 2.

II. Claims 19-23, drawn to formulations of insulins and its analogues, classified in class 514, subclass 3.

III. Claims 24, drawn to formulations of human growth factor, classified in class 514, subclass 2.

IV. Claims 25-27, drawn to formulations of exendin-4 and its analogues, classified in class 514, subclass 2.

V. Claims 28-44, drawn to a method of preparing peptide formulations for an injectable device, classified in class 514, subclass 2.

In response to these requirements, Applicants hereby elect with traverse the invention of Group I, and the species of Arg34, Lys26(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37). Applicants hereby reserve the right to file continuing applications directed to the nonelected subject matter.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this response or application.

Respectfully submitted,

Date: August 14, 2008

/Shelby J. Walker, Reg. No. 45,192/
Shelby J. Walker, Reg. No. 45,192
Novo Nordisk Inc.
Customer Number 23650
(609) 987-4883

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

23650 7590 12/02/2008

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

NOTIFICATION DATE	DELIVERY MODE
12/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
KSHL@novonordisk.com
KISW@novonordisk.com

Office Action Summary	Application No.	Applicant(s)	
	11/435,977	PEDERSEN ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 25-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

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1) ☒ Notice of References Cited (PTO-892)
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3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 12-18, and the species Arg^{34}, Lys^{26}(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), in the reply filed on 08/15/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). A prior art search of Group I and the elected species yielded results that read on claims 1-19, 25-28 and 30-44 (see rejection under 35 U.S.C. 102(e) below). As a result, the restriction requirement between Groups I, II, IV and V is withdrawn. The election of species requirement is maintained. Claims 1-44 are pending. Claims 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim.

Priority

2. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e) based upon U.S. provisional application 60/524,653, filed 11/24/2003. A claim for priority under 35 U.S.C. 119(e) cannot be based on said application, since the instant application was filed more than twelve months thereafter and since PCT/DK04/00792, filed 11/18/2004, does not claim priority to said application.

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

6. The use of the trademarks SEMILENTE, ULTRALENTE, LENTE, LANTUS, ULTRALENTE, HUMALOG, NOVOLOG, NOVOMIX, NOVOPENS and NOVOFINE have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

7. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-19, 25-28 and 30-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Knudsen *et al.* (U.S. 2006/0287221). Knudsen *et al.* teach a pharmaceutical formulation comprising a peptide and propylene glycol present at a final concentration of 14 mg/ml and having a pH of 7.7 (Figures 6-9, paragraphs 0015-0018, examples 3 and 4, paragraphs 0109, 0110), satisfying all of the limitations of claims 1-7. With respect to claim 8, the formulation comprises a preservative, phenol. With respect to claim 9, the preservative phenol is present at a final concentration of 40 mM (3.764 mg/ml). With respect to claim 10, the formulation comprises a buffer. With respect to claim 11, the buffer is bicine (examples 3 and 4, paragraphs

0109, 0110). With respect to claims 12-18, the peptide is the GLP-1 agonist Arg^{34}, Lys^{26}(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) or liraglutide (Figures 6-9, paragraphs 0015-0018, examples 3 and 4, paragraphs 0109, 0110). With respect to claims 12-18, the peptide may also be GLP-1(7-37) (SEQ ID NO. 1), a GLP-1(7-37) analogue, a derivative of GLP-1(7-37), or a derivative of a GLP-1(7-37) analogue; Arg^{34}-GLP-1(7-37), Gly^{8}-GLP-1(7-36)-amide, Gly^{8}-GLP-1(7-37), Val^{8}-GLP-1(7-36)-amide, Val^{8}-GLP-1(7-37), $Val^{8}Asp^{22}$-GLP-1(7-36)-amide, $Val^{8}Asp^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}$-GLP-1(7-36)-amide, $Val^{8}Glu^{22}$-GLP-1(7-37), $Val^{8}Lys^{22}$-GLP-1(7-36)-amide, $Val^{8}Lys^{22}$-GLP-1(7-37), $Val^{8}Arg^{22}$-GLP-1(7-36)-amide, $Val^{8}Arg^{22}$-GLP-1(7-37), $Val^{8}His^{22}$-GLP-1(7-36)-amide, $Val^{8}His^{22}$-GLP-1(7-37), $Val^{8}Trp.sup.19Glu^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}Val^{25}$-GLP-1(7-37), $Val^{8}Tyr^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Leu^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Tyr^{18}Glu^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}His^{37}$-GLP-1(7-37), $Val^{8}Glu^{22}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Val^{25}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Ile^{33}$-GLP-1(7-37), $Val^{8}Glu^{22}Val^{25}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Val^{25}$-GLP-1(7-37), analogues thereof and derivatives of any of these; a GLP-1(7-36)-amide; a derivative of GLP-1(7-37) or a derivative of a GLP-1(7-37) analogue having a lysine residue and wherein a lipophilic substituent optionally via a spacer is attached to the epsilon amino group of said lysine, wherein said lipophilic substituent has from 8 to 40 carbon atoms, and wherein said spacer is present and is selected from an amino acid; a dipeptidyl aminopeptidase IV protected GLP-1 compound; a plasma stable GLP-1 compound; or desamino-His^{7}, Arg^{26}, Lys^{34}(N^{ε}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37), desamino-His^{7}, Arg^{26}, Lys^{34}(N^{ε}-octanoyl)-GLP-1(7-37), Arg^{26}, Lys^{34}, Lys^{38} (N^{ε}-(.omega.-carboxypentadecanoyl))-GLP-1(7-38), Arg^{26},34, Lys^{36}(N^{ε}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1 (7-36) and Arg^{34}, Lys^{26}(N^{ε}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1 (7-37) (paragraphs 0038-

0040, 0064-0066). With respect to claim 19, the formulation also comprises an insulin analogue, insulin Asp$^{\beta 28}$ (aspart) (Figures 6-9, paragraphs 0015-0018, examples 3 and 4, paragraphs 0109, 0110). With respect to claim 19, the peptide may also be a human insulin analogue, Lys $^{\beta 28}$, Pro $^{\beta 29}$-human insulin, Lys $^{\beta 3}$, Glu $^{\beta 29}$-human insulin, des(B30) human insulin or derivative of a human insulin analogue (paragraph 0060). With respect to claims 25-27, the peptide may also be exendin-4, an exendin-4 analogue, a derivative of exendin-4, a derivative of an exendin-4 analogue, exendin-3 or ZP-10 (HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPSKKKKKK-NH2) or an acylated exendin-4 analogue or a pegylated exendin-4 analogue (claims 31-39, paragraph 0068, 0069). With respect to claims 28 and 30-35, Knudsen *et al.* teach a method of making the formulation for injection (Example 1, paragraph 0099, Figures 6-9, paragraphs 0015-0018, examples 3 and 4, paragraphs 0109, 0110). With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent to the prior art of Knudsen *et al.* because the compositions and methods of making them taught by the prior art are identical to the claimed invention. The limitations regarding isotonicity agents previously utilized are mental steps.

10. The applied reference has a common assignee and inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 29 is rejected under 35 U.S.C. 103(a) as being obvious over Knudsen *et al.* (U.S. 2006/0287221). The teaching of Knudsen *et al.* is described above. With respect to claim 29, the reference does not explicitly teach the method steps of preparing a first solution, preparing a second solution. mixing the first and second solutions and adjusting the pH. It would have been obvious to the skilled artisan to make the compositions described in Knudsen *et al.* according to this method.

The applied reference has a common assignee and inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome

by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

13. Claims 1-18, 25-27 and 28-44 are rejected under 35 U.S.C. 103(a) as being obvious over Engelund *et al.* (U.S. 2006/0084605). Engelund *et al.* recites a formulation comprising a GLP-1 peptide, a buffer, a preservative and an isotonicity agent, wherein the pH of the formulation is 7.2-8 (claim 1). Engelund *et al.* teaches that the isotonicity agent may be selected from the group consisting of sodium chloride, xylitol, mannitol, sorbitol, glycerol, glucose, maltose, sucrose, L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine, polyethylene glycol, propylene glycol and mixtures thereof (claim 51). Thus, one of skill in the art could readily envisage a formulation comprising a GLP-1 peptide, a buffer, a preservative and propylene glycol wherein the pH is between 7.2 and 8 based on claims 1 and 51 of Engelund *et al.*. The skilled artisan would have been motivated to optimize the concentration of the isotonicity agent through routine experimentation, satisfying all of the limitations of claims 1-12 and 28-35. With respect to claims 12-18 and 25-27, Engelund *et al.* teach that the GLP-1 peptide may be Arg^{34}, Lys^{26}(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) (claim 28) or an exendin-4 (paragraphs 0065-0067) as well a numerous other GLP-1 analogues (paragraphs 0046-0051). With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent to the compositions and methods of making them that are obvious over the claims of copending Application No. 11/244,497.

The applied reference has a common assignee and inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only

under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-19 and 28-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10, 12, 17-19, 30, 41-49 and 54-72 of copending Application No. 11/417,562. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 1 of copending Application No. 11/417,562 recites a formulation comprising a meal-related insulin, Arg^{34}, Lys^{26}(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), a preservative and an isotonicity agent. Claim 58 of copending Application No. 11/417,562 states that the isotonicity agent may be selected from the group consisting of mannitol, sorbitol, propylene glycol and a mixture thereof. Claims 2 and 3 of copending Application No. 11/417,562 state that the pH of the formulation is from 7 to 9, or from 7 to 8. Thus, one of skill in the art could readily envisage a formulation comprising a peptide, propylene glycol wherein the pH is between 7 and 9 based on claims 1-3 and 58 of copending Application No. 11/417,562. The skilled artisan would have been motivated to optimize the concentration of the isotonicity agent through routine experimentation, satisfying all of the limitations of claims 1-7, 12-19 and 28-35. With respect to claims 8 and 9, claims 1 and 53 of copending Application No. 11/417,562 state that the formulation may also include a preservative selected from phenol and m-cresol. With respect to claims 10 and 11, claim 55 of copending Application No. 11/417,562 state that the formulation may also include a buffer. With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent to the compositions and methods of making them that are obvious over the claims of copending

Application No. 11/417,562. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-18 and 25-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-63 of copending Application No. 11/667,040. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 1 of copending Application No. 11/667,040 recites a formulation comprising an insulinotropic peptide and an isotonicity agent, wherein the pH of the formulation is from 7.0 to 8.5. Claim 25 of copending Application No. 11/667,040 states that the isotonicity agent may be selected from the group consisting of mannitol, glycerol, propylene glycol and a mixture thereof. Thus, one of skill in the art could readily envisage a formulation comprising an insulinotropic peptide and propylene glycol wherein the pH is between 7 and 8.5 based on claim 25 of copending Application No. 11/667,040. The skilled artisan would have been motivated to optimize the concentration of the isotonicity agent through routine experimentation, satisfying all of the limitations of claims 1-7, 12-19 and 28-35. With respect to claims 8 and 9, claim 26 of copending Application No. 11/667,040 state that the formulation may also include a preservative. With respect to claims 10 and 11, claims 22-24 of copending Application No. 11/667,040 state that the formulation may also include a buffer. With respect to claims 12-18, claim 31 of copending Application No. 11/667,040 states that the insulinotropic peptide is Arg^{34}, Lys^{26}(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37). With respect to claims 12-16, 18 and 25-27, claims 27-30 and 32-35 of copending Application 11/667,040 state the insulinotropic peptide may be one of numerous GLP-1 analogues or derivatives or exendin

analogues or derivatives. With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent to the compositions and methods of making them that are obvious over the claims of copending Application No. 11/667,040. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-12 and 28-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-11, 19-21, 29 and 48-54 of copending Application No. 11/244,497. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 1 of copending Application No. 11/244,497 recites a formulation comprising a GLP-1 peptide, a buffer, a preservative and an isotonicity agent, wherein the pH of the formulation is 7.2-8. Claim 51 of copending Application No. 11/244,497 states that the isotonicity agent may be selected from the group consisting of sodium chloride, xylitol, mannitol, sorbitol, glycerol, glucose, maltose, sucrose, L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine, polyethylene glycol, propylene glycol and mixtures thereof. Thus, one of skill in the art could readily envisage a formulation comprising a GLP-1 peptide, a buffer, a preservative and propylene glycol wherein the pH is between 7.2 and 8 based on claims 1 and 51 of copending Application No. 11/244,497. The skilled artisan would have been motivated to optimize the concentration of the isotonicity agent through routine experimentation, satisfying all of the limitations of claims 1-7, 12 and 28-35. With respect to claims 8 and 9, claim 49 of copending Application No. 11/244,497 recites a list of possible preservatives. With respect to claims 10 and 11, claim 48 of copending

Application No. 11/244,497 recites a list of possible buffers. With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent to the compositions and methods of making them that are obvious over the claims of copending Application No. 11/244,497. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

20. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

Notice of References Cited	Application/Control No. 11/435,977	Applicant(s)/Patent Under Reexamination PEDERSEN ET AL.	
	Examiner Christina Marchetti Bradley	Art Unit 1654	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2006/0287221	12-2006	Knudsen et al.	514/003
*	B	US-2006/0084605	04-2006	Engelund et al.	514/012
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11435977	PEDERSEN ET AL.
	Examiner	Art Unit
	Christina Marchetti Bradley	1654

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/19/2008								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
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	30	✓								
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	32	✓								
	33	✓								
	34	✓								
	35	✓								
	36	✓								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11435977	PEDERSEN ET AL.
	Examiner	**Art Unit**
	Christina Marchetti Bradley	1654

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/19/2008								
	37	✓								
	38	✓								
	39	✓								
	40	✓								
	41	✓								
	42	✓								
	43	✓								
	44	✓								

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al.

Application No.: 11/435,977 Group Art Unit: 1646

Filed: May 17, 2006 Examiner: TBA

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with 37 C.F.R. 1.56, 1.97 and 1.98, Applicants submit herewith references which they believe may be material to the patentability of this application and with respect to which there may be a duty to disclose in accordance with 37 C.F.R. 1.56.

While the references may be "material" under 37 C.F.R. 1.56, it is not intended to constitute an admission that the references are "prior art" unless specifically designated as such.

The filing of this Information Disclosure Statement shall not be construed as a representation that no material references other than those listed exist or that a search has been conducted.

The references are listed in Form PTO-1449 which is in accordance with the requirements of M.P.E.P. 609. A copy of the references is also enclosed.

The references are as follows:

1. WO 2005/046716
2. WO 93/23010
3. WO 95/13825
4. WO 99/16417
5. U.S. Patent No. 2002/0151467

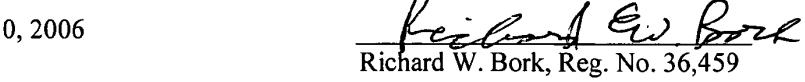
6. WO 03/013589
7. EP 1424077
8. U.S. Patent No.5206219
9. WO 95/22560
10. WO 95/05848
11. WO 02/067989
12. WO 92/19260
13. Sing, S et al – AAPS Pharmscitech – 2003 – Vol. 4 Part 3 – Pgs. 334-342

It is respectfully requested that these references be considered by the Patent and Trademark Office in its examination of the above-identified application and be made of record therein. The Examiner is also invited to contact the undersigned if there are any questions concerning this paper or the attached references.

The information disclosure statement submitted herewith is being filed **within** three months of the filing date of a national application or date of entry into the national stage of an international application or **before** the mailing date of a first Office action on the merits, or **before** the mailing date of a first Office action after the filing of a request for continued examination. Therefore, no fee is due. However, please charge any fees should they be required, to Novo Nordisk Inc. Deposit Account No. 14-1447.

Respectfully submitted,

Date: July 10, 2006



Richard W. Bork, Reg. No. 36,459
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(609) 987-5800

Use the following customer number for all correspondence regarding this application.

23650
PATENT TRADEMARK OFFICE

FORM PTO-1449 (Rev. 2-32)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	Atty. Docket No. 6683.204-US	Serial No. 11/435,977
	INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	Applicant Pedersen et al.	
		Filing Date May 17, 2006	Group 1646

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		2002/0151467	12/21/00	Leung, F.K.			
		5206219	11/25/91	Applied Analytical Industries, INC			

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		2005/046716	11/12/04	WO				
		93/23010	05/07/92	WO				
		95/13825	10/24/94	WO				
		99/16417	10/01/97	WO				
		03/013589	05/20/02	WO				
		1424077	05/20/02	EP				
		95/22560	02/21/95	WO				
		95/05848	08/23/94	WO				
		02/067989	01/08/02	WO				
		92/19260	05/07/91	WO				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

			Singh, S et al - Aaps Pharmscitech - 2003 - Vol. 4 - Part 3-Pgs.334-342

EXAMINER /Christina Bradley/ DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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     FILE 'CAPLUS' ENTERED AT 14:27:01 ON 19 NOV 2008
L1             1 S US  20070010424/PN
L2         32637 S PROPYLENE GLYCOL
L3        187137 S INSULIN
L4          1146 S GLUCAGON-LIKE PEPTIDE I
L5          2965 S GLP?
L6           689 S EXENDIN
L7        207001 S DRUG DELIVERY SYSTEMS
L8         82033 S FORMULATION
L9           158 S L2 AND (L3-L6) AND (L7 OR L8)
L10            6 S L2 (L) (L3-L6) (L) (L7 OR L8)

     FILE 'STNGUIDE' ENTERED AT 14:30:02 ON 19 NOV 2008

     FILE 'CAPLUS' ENTERED AT 14:31:38 ON 19 NOV 2008
L11            3 S L2 AND L3 AND (L4 OR L5) AND L6 AND (L7 OR L8)
L12           11 S L2 AND L3 AND (L4-L6) AND (L7 OR L8)
L13            2 S L2(L)(L4-L6)(L)(L7 OR L8)
L14           15 S L2 AND (L4-L6) AND (L7 OR L8)

     FILE 'STNGUIDE' ENTERED AT 14:33:45 ON 19 NOV 2008

     FILE 'CAPLUS' ENTERED AT 14:36:17 ON 19 NOV 2008
L15            5 S L2 (L) L3 (L) (L7 OR L8)

     FILE 'CAPLUS' ENTERED AT 14:38:52 ON 19 NOV 2008
L16        15664 S (PEPTIDE OR PROTEIN)(L) (L7 OR L8)
L17            1 S L16 AND L1
L18            0 S (PEPTIDE OR PROTEIN)(L) (L1)
L19            1 S (PEPTIDE OR PROTEIN) AND (L7 OR L8) AND L1
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Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed December 2, 2008, please amend the above-captioned application and consider the remarks herewith as follows:

AMENDMENTS TO THE SPECIFICATION begin on page 2 of this paper.

AMENDMENTS TO THE CLAIMS are reflected in the Listing of Claims which begins on page 4 of this paper.

REMARKS begin on page 10 of this paper.

AMENDMENTS TO THE SPECIFICATION:

Please replace page 10, lines 30-33 with the following:

--(SEMILENTE®) with extended insulin zinc (ULTRALENTE®), sold commercially as LENTE®, insulin glargine (LANTUS®) or extended insulin zinc (ULTRALENTE®), Lys^{B28} Pro^{B29} human insulin (HUMALOG®) , Asp^{B28} human insulin, insulin aspart (NOVOLOG®), or a 30/70 mixture of insulin aspart and insulin aspart protamine (NOVOMIX®) .—

Please replace page 22, lines 13-18 with the following:

--In this test 10 NOVOPENS® 1.5 ml mounted with NOVOFINE 30® G (G 30 needle) were tested for each formulation, 5 of them placed in upright and 5 in horizontal position. The Pensystems were stored at room temperature in between testing. Each day the needle was examined for deposits and an air shot was performed prior to injection into a tissue. Degree of resistance and clogging, if any, was noted. Injections were made on a daily basis with the same needle, and this was done for 9 working days for all the formulations.—

Please replace page 2, lines 11-24 with the following:

--The NOVOMIX® 30-containing formulation was prepared as follows:

a) Prepared a solution by dissolving buffer, sodium chloride, phenol, mannitol and sodium hydroxide in water

b) Prepared a solution of sodium chloride, phenol and mannitol in water

c) Prepared a solution of protamine sulphate in water

d) Prepared a solution of insulin, hydrochloric acid and zinc in water

e) Solutions b), c) and d) were mixed

f) Solution e) was added to the solution of step a)

g) Adjustedthe pH of the solution to the desired pH and crystallized at room temperature

h) Prepared a solution by dissolving m-cresol, phenol and mannitol in water

i) Solution h) is added to the crystalline fraction of step g); and

j) Adjusted the pH to the desired pH

The composition of the NOVOMIX® 30-containing formulation prepared in the above manner was as follows:--

Please replace page 29, lines 11-26 with the following:

--Example 6

Testing of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 formulations containing propylene glycol

The preparation and composition of the Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 formulations will be as described in Example 5 except that mannitol will be replaced with a concentration of propylene glycol that assures tonicity. A simulated in use test will then be conducted as described in Example 5.

Based on the fact that the clogging effect of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 mannitol-containing formulations was similar to that observed with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) mannitol-containing formulations, it is believed that the effect of propylene glycol on the clogging effect of Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30-containing formulations will be similar to that observed with Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations.--

AMENDMENTS TO THE CLAIMS:

The following Listing of Claims replaces all prior versions, and listings, of claims.

LISTING OF CLAIMS

1. (Original) A pharmaceutical formulation comprising at least one peptide and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.

2. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

3. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

4. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

5. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 9.5.

6. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.

7. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.3 to about 8.3.

8. (Original) The formulation according to claim 1, further comprising a preservative.

9. (Original) The formulation according to claim 8, wherein said preservative is present in a concentration from 0.1mg/ml to 20mg/ml.

10. (Original) The formulation according to claim 1, further comprising a buffer.

11. (Original) The formulation according to claim 10, wherein said buffer is selected from the group consisting of glycylglycine, L-histidine, Hepes, bicine and disodium phosphate dihydrate.

12. (Original) The formulation according to claim 1, wherein said peptide is a GLP-1 agonist.

13. (Original) The formulation according to claim 12, wherein said GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

14. (Original) The formulation according to claim 13, wherein said GLP-1 agonist is a derivative of GLP-1(7-36) or GLP-1(7-37) or a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, where said derivative has a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine.

15. (Original) The formulation according to claim 14, wherein said lipophilic substituent has from 8 to 40 carbon atoms.

16. (Original) The formulation according to claim 15, wherein said spacer is an amino acid.

17. (Original) The formulation according to claim 16, wherein said GLP-1 agonist is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

18. (Original) The formulation according to claim 12, wherein said GLP-1 agonist is selected from the group consisting of Gly^8-GLP-1(7-36)-amide, Gly^8-GLP-1(7-37), Val^8-GLP-1(7-36)-amide, Val^8-GLP-1(7-37), Val^8Asp^{22}-GLP-1(7-36)-amide, Val^8Asp^{22}-GLP-1(7-37) , Val^8Glu^{22}-GLP-1(7-36)-amide , Val^8Glu^{22}-GLP-1(7-37), Val^8Lys^{22}-GLP-1(7-36)-amide, Val^8Lys^{22}-GLP-1(7-37), Val^8Arg^{22}-GLP-1(7-36)-amide, Val^8Arg^{22}-GLP-1(7-37), Val^8His^{22}-GLP-1(7-36)-amide,

$Val^{8}His^{22}$-GLP-1(7-37), Arg34GLP-1(7-37); Arg26,34,Lys36GLP-1(7-36); Arg26GLP-1(7-37); and Gly8,Arg26,34,Glu37,Lys38GLP-1(7-38) analogues thereof and derivatives of any of these.

19. (Original) The formulation according to claim 1, wherein said peptide is selected from insulin, an insulin analogue, a derivative of insulin or an insulin analogue or a mixture of any of the foregoing.

20. (Withdrawn) The formulation according to claim 19, wherein said peptide is an insulin derivative in which said derivative contains a lysine residue to which a lipophilic substituent of at least six carbon atoms is attached.

21. (Withdrawn) The formulation according to claim 20, wherein the insulin derivative is Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin.

22. (Withdrawn) The formulation according to claim 20, wherein said insulin derivative is $N^{\square B29}$-octanoyl insulin.

23. (Withdrawn) The formulation according to claim 19, wherein said peptide is a 30/70 mixture of insulin aspart and insulin aspart protamine.

24. (Withdrawn) The formulation according to claim 1, wherein said peptide is human growth hormone (hGH) or Met-hGH.

25. (Original) The formulation according to claim 24, wherein said peptide is exendin 4, an exendin 4 analogue or a derivative of exendin 4 or an exendin 4 analogue.

26. (Original) The formulation according to claim 25, wherein said peptide is exendin 4.

27. (Original) The formulation according to claim 25, wherein said peptide is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPSKKKKKK-amide.

28. (Original) A method of preparing a peptide formulation suitable for use in an injection device, said method comprising preparing a formulation containing peptide and propylene glycol and optionally a buffer and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from about 7.0 to about 10.0.

29. (Original) The method according to claim 28, wherein said peptide, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;
b) preparing a second solution by dissolving the peptide in water;
c) mixing the first and second solutions; and
d) adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

30. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

31. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

32. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

33. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 9.5.

34. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 8.0.

35. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.2 to about 8.0.

36. (Original) A method for reducing deposits on production equipment during production of a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

37. (Original) The method according to claim 36, wherein the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

38. (Original) The method according to claim 36, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

39. (Original) A method for reducing deposits in the final product during production of a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

40. (Original) The method according to claim 39, wherein the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

41. (Original) The method according to claim 39, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, glycerol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

42. (Original) A method for reducing the clogging of injection devices by a peptide formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

43. (Original) The method according to claim 42, wherein the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

44. (Original) The method according to claim 42, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

REMARKS

Upon entry of the present amendment, claims 1 – 19 and 25 - 44 are pending. The present amendment adds no new matter.

THE REJECTION UNDER 35 U.S.C. §102(E)

The Office Action rejected claims 1-19, 25-28 and 30-44 under 35 U.S.C. §102(e) as being anticipated by Knudsen et al. (U.S. 2006/0287221; "**Knudsen**").

Applicants note that the present Application is a continuation of PCT Application No. DK2004/000792 (filed on November 18, 2004). In addition, the present Application claims priority under 35 U.S.C. §119(a-d) to Danish Patent Application No. PA 200301719 (filed November 20, 2003). Thus, the present Application is entitled at least to the **November 20, 2003** priority date. In contrast, **Knudsen** is a continuation of PCT Application No. DK2004/000788 (filed on November 12, 2004). Thus, the effective US filing date of **Knudsen** is May 3, 2006. In light of the foregoing, Applicants note that, as set forth in M.P.E.P. §2136.03, a reference's foreign priority date under 35 U.S.C. §119(a)-(d) and (f) can not be used as the 35 U.S.C. §102(e) reference date, and thus, cannot be used to antedate the present Application's filing date. *See e.g. In re Hilmer*, 359 F.2d 859, 149 USPQ 480 (CCPA 1966) (*Hilmer I*) (Applicant filed an application with a right of priority to a German application. The examiner rejected the claims over a U.S. patent to Habicht based on its Swiss priority date. The U.S. filing date of Habicht was later than the application's German priority date. The court held that the reference's Swiss priority date could not be relied on in a 35 U.S.C. 102(e) rejection. Because the U.S. filing date of Habicht was later than the earliest effective filing date (German priority date) of the application, the rejection was reversed.). Accordingly, Applicants believe that the present rejection is now moot.

The Rejections under 35 U.S.C. §103(a)

The Examiner has rejected claim 29 under 35 U.S.C. §103(a) as being obvious over **Knudsen**.

Applicants note that the present Application and **Knudsen** were, at the time the invention of the present Application was made, owned by Novo Nordisk. Thus, Applicants assert that **Knudsen** is disqualified under 35 U.S.C. §103(c) as prior art in the present rejection under 35 U.S.C. §103(a).

See e.g. M.P.E.P. §706.02(l)(2)(II). Accordingly, Applicants believe that the present rejection is now moot.

The Examiner has also rejected claims 1-18, 25-27 and 28-44 under 35 U.S.C. §103(a) as being obvious over Engelund et al. (U.S. 2006/0084605; "**Engelund**").

Applicants note that the present Application and **Engelund** were, at the time the invention of the present Application was made, owned by Novo Nordisk. Thus, Applicants assert that **Engelund** is disqualified under 35 U.S.C. §103(c) as prior art in the present rejection under 35 U.S.C. §103(a). *See e.g.* M.P.E.P. §706.02(l)(2)(II). Accordingly, Applicants believe that the present rejection is now moot.

THE NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

The Examiner has made the following provisional rejections on the grounds of nonstatutory obviousness-type double patenting:

1) Claims 1-19 and 28-44 are rejected as being unpatentable over claims 1-8, 10, 12, 17-19, 30, 41-49 and 54-72 of copending US Patent Application No. 11/417,562;
2) Claims 1-18 and 25-44 are rejected as being unpatentable over claims 1-63 of copending US Patent Application No. 11/667,040; and
3) Claims 1-12 and 28-44 are rejected as being unpatentable over claims 1, 3-11, 19-21 29 and 48-54 of copending US Patent Application No. 11/244,497.

Applicants note that upon the issuance of any the above referenced applications, Applicants will review the need for Terminal Disclaimers in the remaining, pending applications upon notification of allowable subject matter in the same. Accordingly, Applicants believe that the present rejection is now moot.

CONCLUSION

In view of the above, Applicant(s) submit(s) that the application is now in condition for allowance and issue and respectfully request(s) early action to that end. Applicant(s) believe(s) that no additional fees are due. However, should any fees be due, the Commissioner is hereby authorized to charge any fees in connection with this application and to credit any overpayments to Deposit Account No. 14-1447. The undersigned invites the Examiner to contact him/her by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: April 2, 2009

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

23650 7590 06/25/2009

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

NOTIFICATION DATE	DELIVERY MODE
06/25/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
KSHL@novonordisk.com
KISW@novonordisk.com

Office Action Summary	Application No.	Applicant(s)	
	11/435,977	PEDERSEN ET AL.	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,25-28 and 30-44* is/are rejected.

7)☒ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-44 are pending. Claims 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim.

Priority

2. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e) based upon U.S. provisional application 60/524,653, filed 11/24/2003. A claim for priority under 35 U.S.C. 119(e) cannot be based on said application, since the instant application was filed more than twelve months thereafter and since PCT/DK04/00792, filed 11/18/2004, does not claim priority to said application.

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

6. The objection to the use of the trademarks SEMILENTE, ULTRALENTE, LENTE, LANTUS, ULTRALENTE, HUMALOG, NOVOLOG, NOVOMIX, NOVOPENS and NOVOFINE is withdrawn in light of the amendment filed 04/02/2009.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-19, 25-28 and 30-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Knudsen *et al.* (U.S. 2006/0287221). Knudsen *et al.* teach a pharmaceutical formulation comprising a peptide and propylene glycol present at a final concentration of 14 mg/ml and having a pH of 7.7 (Figures 6-9, paragraphs 0015-0018, examples 3 and 4, paragraphs 0109, 0110), satisfying all of the limitations of claims 1-7. With respect to claim 8, the formulation comprises a preservative, phenol. With respect to claim 9, the preservative phenol is present at a final concentration of 40 mM (3.764 mg/ml). With respect to claim 10, the formulation comprises a buffer. With respect to claim 11, the buffer is bicine (examples 3 and 4, paragraphs 0109, 0110). With respect to claims 12-18, the peptide is the GLP-1 agonist Arg^{34}, Lys^{26}(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) or liraglutide (Figures 6-9, paragraphs 0015-0018, examples 3 and 4, paragraphs 0109, 0110). With respect to claims 12-18, the peptide may also be GLP-1(7-37) (SEQ ID NO. 1), a GLP-1(7-37) analogue, a derivative of GLP-1(7-37), or a derivative of a GLP-1(7-37) analogue; Arg^{34}-GLP-1(7-37), Gly^{8}-GLP-1(7-36)-amide, Gly^{8}-GLP-1(7-37), Val^{8}-GLP-1(7-36)-amide, Val^{8}-GLP-1(7-37), $Val^{8}Asp^{22}$-GLP-1(7-36)-amide, $Val^{8}Asp^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}$-GLP-1(7-36)-amide, $Val^{8}Glu^{22}$-GLP-1(7-37), $Val^{8}Lys^{22}$-GLP-1(7-36)-amide, $Val^{8}Lys^{22}$-GLP-1(7-37), $Val^{8}Arg^{22}$-GLP-1(7-36)-amide, $Val^{8}Arg^{22}$-GLP-1(7-37), $Val^{8}His^{22}$-GLP-1(7-36)-amide, $Val^{8}His^{22}$-GLP-1(7-37), Val^{8}Trp.sup.19Glu^{22}-GLP-1(7-37), $Val^{8}Glu^{22}Val^{25}$-GLP-1(7-37), $Val^{8}Tyr^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Leu^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Tyr^{18}Glu^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}His^{37}$-GLP-1(7-37), $Val^{8}Glu^{22}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Val^{25}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Ile^{33}$-GLP-1(7-37), $Val^{8}Glu^{22}Val^{25}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Val^{25}$-GLP-1(7-37), analogues thereof

and derivatives of any of these; a GLP-1(7-36)-amide; a derivative of GLP-1(7-37) or a derivative of a GLP-1(7-37) analogue having a lysine residue and wherein a lipophilic substituent optionally via a spacer is attached to the epsilon amino group of said lysine, wherein said lipophilic substituent has from 8 to 40 carbon atoms, and wherein said spacer is present and is selected from an amino acid; a dipeptidyl aminopeptidase IV protected GLP-1 compound; a plasma stable GLP-1 compound; or desamino-His^{7}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-(γ-Glu(N$^{\alpha}$-hexadecanoyl)))-GLP-1(7-37), desamino-His^{7}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl)-GLP-1(7-37), Arg^{26}, Lys^{34}, Lys^{38} (N$^{\varepsilon}$-(.omega.-carboxypentadecanoyl))-GLP-1(7-38), Arg^{26},34, Lys^{36}(N$^{\varepsilon}$-(γ-Glu(N$^{\alpha}$-hexadecanoyl)))-GLP-1 (7-36) and Arg^{34}, Lys^{26}(N$^{\varepsilon}$-(γ-Glu(N$^{\alpha}$-hexadecanoyl)))-GLP-1 (7-37) (paragraphs 0038-0040, 0064-0066). With respect to claim 19, the formulation also comprises an insulin analogue, insulin Asp$^{\beta 28}$ (aspart) (Figures 6-9, paragraphs 0015-0018, examples 3 and 4, paragraphs 0109, 0110). With respect to claim 19, the peptide may also be a human insulin analogue, Lys $^{\beta 28}$, Pro $^{\beta 29}$-human insulin, Lys $^{\beta 3}$, Glu $^{\beta 29}$-human insulin, des(B30) human insulin or derivative of a human insulin analogue (paragraph 0060). With respect to claims 25-27, the peptide may also be exendin-4, an exendin-4 analogue, a derivative of exendin-4, a derivative of an exendin-4 analogue, exendin-3 or ZP-10 (HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPSKKKKKK-NH2) or an acylated exendin-4 analogue or a pegylated exendin-4 analogue (claims 31-39, paragraph 0068, 0069). With respect to claims 28 and 30-35, Knudsen *et al.* teach a method of making the formulation for injection (Example 1, paragraph 0099, Figures 6-9, paragraphs 0015-0018, examples 3 and 4, paragraphs 0109, 0110). With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent to the prior art of Knudsen *et al.* because the compositions and

methods of making them taught by the prior art are identical to the claimed invention. The limitations regarding isotonicity agents previously utilized are mental steps.

9. The applied reference has a common assignee and inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

10. In the response filed 04/02/2009, Applicant traverses the rejection on the grounds that the applied reference does not qualify as prior art under 35 U.S.C. 102(e). This argument is not persuasive.

11. All references, whether the WIPO publication, the U.S. patent application publication or the U.S. patent of, or claiming the benefit of, an international application (IA) that was filed on or after November 29, 2000, designated the U.S., and was published in English under PCT Article 21(2) have the 35 U.S.C. 102(e) prior art date of the international filing date or earlier effective U.S. filing date. U.S. 2006/0287221 is a continuation of PCT/DK04/00788 which claims priority to US provisional application 60/519,590, filed November 13, 2003. PCT/DK/04/00788 was filed after November 29, 2000, designated the U.S., and was published in English. Therefore, the prior art date for U.S. 2006/0287221 is November 13, 2003 which is prior to the foreign priority date of the instant application November 20, 2003. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

12. The rejection of claim 29 under 35 U.S.C. 103(a) as being obvious over Knudsen *et al.* (U.S. 2006/0287221) is withdrawn. Applicant has provided evidence in this file showing that the invention was owned by, or subject to an obligation of assignment to, the same entity as Knudsen *et al.* (U.S. 2006/0287221) at the time this invention was made. Therefore, Knudsen *et al.* (U.S. 2006/0287221) is disqualified as prior art under 35 U.S.C. 103(c).

13. The rejection of claims 1-18, 25-27 and 28-44 under 35 U.S.C. 103(a) as being obvious over Engelund *et al.* (U.S. 2006/0084605) is withdrawn. Applicant has provided evidence in this file showing that the invention was owned by, or subject to an obligation of assignment to, the same entity as Engelund *et al.* (U.S. 2006/0084605) at the time this invention was made. Therefore, Engelund *et al.* (U.S. 2006/0084605) is disqualified as prior art under 35 U.S.C. 103(c).

Allowable Subject Matter

14. Claim 29 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-19 and 28-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10, 12, 17-19, 30, 41-49 and 54-72 of copending Application No. 11/417,562. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 1 of copending Application No. 11/417,562 recites a formulation comprising a meal-related insulin, Arg^{34}, Lys^{26}(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), a preservative and an isotonicity agent. Claim 58 of copending Application No. 11/417,562 states that the isotonicity agent may be selected from the group consisting of mannitol, sorbitol, propylene glycol and a mixture thereof. Claims 2 and 3 of copending Application No. 11/417,562 state that the pH of the formulation is from 7 to 9, or from 7 to 8. Thus, one of skill in the art could readily envisage a formulation comprising a peptide, propylene glycol wherein the pH is between 7 and 9 based on claims 1-3 and 58 of copending Application No. 11/417,562. The skilled artisan would have been motivated to optimize the concentration of the isotonicity agent through routine experimentation, satisfying all of the limitations of claims 1-7, 12-19 and 28-35. With respect to claims 8 and 9, claims 1 and 53 of copending Application No. 11/417,562 state that the formulation may also include a preservative selected from phenol and m-cresol. With respect to claims 10 and 11, claim 55 of copending Application No. 11/417,562 state that the formulation may also include a buffer. With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent

to the compositions and methods of making them that are obvious over the claims of copending Application No. 11/417,562. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-18 and 25-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-63 of copending Application No. 11/667,040. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 1 of copending Application No. 11/667,040 recites a formulation comprising an insulinotropic peptide and an isotonicity agent, wherein the pH of the formulation is from 7.0 to 8.5. Claim 25 of copending Application No. 11/667,040 states that the isotonicity agent may be selected from the group consisting of mannitol, glycerol, propylene glycol and a mixture thereof. Thus, one of skill in the art could readily envisage a formulation comprising an insulinotropic peptide and propylene glycol wherein the pH is between 7 and 8.5 based on claim 25 of copending Application No. 11/667,040. The skilled artisan would have been motivated to optimize the concentration of the isotonicity agent through routine experimentation, satisfying all of the limitations of claims 1-7, 12-19 and 28-35. With respect to claims 8 and 9, claim 26 of copending Application No. 11/667,040 state that the formulation may also include a preservative. With respect to claims 10 and 11, claims 22-24 of copending Application No. 11/667,040 state that the formulation may also include a buffer. With respect to claims 12-18, claim 31 of copending Application No. 11/667,040 states that the insulinotropic peptide is Arg^{34}, Lys^{26}(N-ε-(7-Glu(N-α-hexadecanoyl)))-GLP-1(7-37). With respect to claims 12-16, 18 and 25-27, claims 27-30 and 32-35 of copending Application 11/667,040 state the

insulinotropic peptide may be one of numerous GLP-1 analogues or derivatives or exendin analogues or derivatives. With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent to the compositions and methods of making them that are obvious over the claims of copending Application No. 11/667,040. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1-12 and 28-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-11, 19-21, 29 and 48-54 of copending Application No. 11/244,497. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 1 of copending Application No. 11/244,497 recites a formulation comprising a GLP-1 peptide, a buffer, a preservative and an isotonicity agent, wherein the pH of the formulation is 7.2-8. Claim 51 of copending Application No. 11/244,497 states that the isotonicity agent may be selected from the group consisting of sodium chloride, xylitol, mannitol, sorbitol, glycerol, glucose, maltose, sucrose, L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine, polyethylene glycol, propylene glycol and mixtures thereof. Thus, one of skill in the art could readily envisage a formulation comprising a GLP-1 peptide, a buffer, a preservative and propylene glycol wherein the pH is between 7.2 and 8 based on claims 1 and 51 of copending Application No. 11/244,497. The skilled artisan would have been motivated to optimize the concentration of the isotonicity agent through routine experimentation, satisfying all of the limitations of claims 1-7, 12 and 28-35. With respect to claims 8 and 9, claim 49 of copending Application No. 11/244,497 recites a

list of possible preservatives. With respect to claims 10 and 11, claim 48 of copending Application No. 11/244,497 recites a list of possible buffers. With respect to claims 36-44, the effect of reducing deposits on production equipment is inherent to the compositions and methods of making them that are obvious over the claims of copending Application No. 11/244,497. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Applicant did not traverse the double patenting rejections in the response filed 04/02/2009. Therefore, the rejections are maintained.

Conclusion

20. No claims are allowed.

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 8:30 A.M. to 4:30 P.M.

23. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

RESPONSE TO FINAL OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Final Office Action mailed June 25, 2009, please amend the above-captioned application and consider the remarks herewith as follows:

AMENDMENTS TO THE CLAIMS are reflected in the Listing of Claims which begins on page 2 of this paper.

REMARKS begin on page 8 of this paper.

AMENDMENTS TO THE CLAIMS:

The following Listing of Claims replaces all prior versions, and listings, of claims.

LISTING OF CLAIMS

1. (Currently Amended) A pharmaceutical formulation comprising at least one ~~peptide~~ GLP-1 agonist, a disodium phosphate dehydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.

2. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

3. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

4. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

5. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 9.5.

6. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.

7. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.3 to about 8.3.

8. (Original) The formulation according to claim 1, further comprising a preservative.

9. (Original) The formulation according to claim 8, wherein said preservative is present in a concentration from 0.1mg/ml to 20mg/ml.

10. (Cancelled).

11. (Cancelled).

12. (Cancelled).

13. (Original) The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

14. (Original) The formulation according to claim 13, wherein said GLP-1 agonist is a derivative of GLP-1(7-36) or GLP-1(7-37) or a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, where said derivative has a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine.

15. (Original) The formulation according to claim 14, wherein said lipophilic substituent has from 8 to 40 carbon atoms.

16. (Original) The formulation according to claim 15, wherein said spacer is an amino acid.

17. (Original) The formulation according to claim 16, wherein said GLP-1 agonist is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

18. (Original) The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of Gly^8-GLP-1(7-36)-amide, Gly^8-GLP-1(7-37), Val^8-GLP-1(7-36)-amide, Val^8-GLP-1(7-37), Val^8Asp^{22}-GLP-1(7-36)-amide, Val^8Asp^{22}-GLP-1(7-37) , Val^8Glu^{22}-GLP-1(7-36)-amide , Val^8Glu^{22}-GLP-1(7-37), Val^8Lys^{22}-GLP-1(7-36)-amide, Val^8Lys^{22}-GLP-1(7-37), Val^8Arg^{22}-GLP-1(7-36)-amide, Val^8Arg^{22}-GLP-1(7-37), Val^8His^{22}-GLP-1(7-36)-amide, Val^8His^{22}-GLP-1(7-37), Arg34GLP-1(7-37); Arg26,34,Lys36GLP-1(7-36); Arg26GLP-1(7-37); and

Gly8,Arg26,34,Glu37,Lys38GLP-1(7-38) analogues thereof and derivatives of any of these.

19. (Cancelled).

20. (Withdrawn) The formulation according to claim 19, wherein said peptide is an insulin derivative in which said derivative contains a lysine residue to which a lipophilic substituent of at least six carbon atoms is attached.

21. (Withdrawn) The formulation according to claim 20, wherein the insulin derivative is Lys ß29 (Nε-tetradecanoyl) des(B30) human insulin.

22. (Withdrawn) The formulation according to claim 20, wherein said insulin derivative is N^{LB29}-octanoyl insulin.

23. (Withdrawn) The formulation according to claim 19, wherein said peptide is a 30/70 mixture of insulin aspart and insulin aspart protamine.

24. (Withdrawn) The formulation according to claim 1, wherein said peptide is human growth hormone (hGH) or Met-hGH.

25. (Cancelled).

26. (Cancelled).

27. (Cancelled).

28. (Currently Amended) A method of preparing a peptide formulation suitable for use in an injection device, said method comprising preparing a formulation containing peptide and propylene glycol and optionally a buffer and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from

about 7.0 to about 10.0, and wherein said peptide, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;

b) preparing a second solution by dissolving the peptide in water;

c) mixing the first and second solutions; and

adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

29. (Cancelled).

30. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

31. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

32. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

33. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 9.5.

34. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 8.0.

35. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.2 to about 8.0.

36. (Currently Amended) A method for reducing deposits on production equipment during production of a ~~peptide~~ GLP-1 agonist formulation, said method comprising replacing the isotonicity

agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dehydrate buffer.

37. (Original) The method according to claim 36, wherein the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

38. (Original) The method according to claim 36, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

39. (Currently Amended) A method for reducing deposits in the final product during production of a ~~peptide~~ GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dehydrate buffer.

40. (Original) The method according to claim 39, wherein the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

41. (Original) The method according to claim 39, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, glycerol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

42. (Currently Amended) A method for reducing the clogging of injection devices by a ~~peptide~~

GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dehydrate buffer.

43. (Original) The method according to claim 42, wherein the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

44. (Original) The method according to claim 42, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

REMARKS

Upon entry of the present amendment, claims 1 – 9, 13 – 18, 28 and 30 - 44 are pending. Claims 10 – 12, 19, 25 – 27 and 29 have been cancelled. Claims 20 – 24 have been withdrawn. Claims 1, 36, 39 and 42 have been amended to now recite a pharmaceutical formulation comprising at least one GLP-1 agonist, propylene glycol and a disodium phosphate dehydrate buffer. Basis may e.g. be found in the claims as originally filed (i.e. claims 10, 11 and 12) and in the Specification on pg. 5, lines 18-19 and pg. 13, lines 25, 26-27 and 32. Claim 28 has been amended to recite the limitations of claim 29. The present amendment adds no new matter.

THE REJECTION UNDER 35 U.S.C. §102(E)

The Office Action rejected claims 1-19, 25-28 and 30-44 under 35 U.S.C. §102(e) as being anticipated by Knudsen et al. (U.S. 2006/0287221; "**Knudsen**").

Applicants have amended claims 1, 36, 39 and 42 to recite a pharmaceutical formulation comprising at least one GLP-1 agonist, propylene glycol and a disodium phosphate dehydrate buffer. Basis may e.g. be found in the claims as originally filed (i.e. claims 10, 11 and 12) and in the Specification on pg. 5, lines 18-19 and pg. 13, lines 25, 26-27 and 32. Applicants note that **Knudsen** is related to pharmaceutical compositions comprising a mixture of an insulin peptide and a GLP-1 peptide; compositions described include those comprising insulin aspart, liraglutide, propylene glycol and phenol. However, nowhere is a pharmaceutical formulation mentioned which comprises at least one GLP-1 agonist, about 1 mg/ml to about 100 mg/ml propylene glycol and a disodium phosphate dehydrate buffer, wherein said formulation has a pH of from about 7.0 to about 10.0. For example, neither the Specification, nor any of the examples in **Knudsen** mention a composition comprising a disodium phosphate dehydrate buffer, a method of preparing such or method of reducing deposits or clogging. Accordingly, Applicants believe that the present rejection is now moot.

THE NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

The Examiner has made the following provisional rejections on the grounds of nonstatutory obviousness-type double patenting:

1) Claims 1-19 and 28-44 are rejected as being unpatentable over claims 1-8, 10, 12, 17-19, 30, 41-49 and 54-72 of copending US Patent Application No. 11/417,562;
2) Claims 1-18 and 25-44 are rejected as being unpatentable over claims 1-63 of copending US Patent Application No. 11/667,040; and
3) Claims 1-12 and 28-44 are rejected as being unpatentable over claims 1, 3-11, 19-21 29 and 48-54 of copending US Patent Application No. 11/244,497.

Applicants note that upon the issuance of any the above referenced applications, Applicants will review the need for Terminal Disclaimers in the remaining, pending applications upon notification of allowable subject matter in the same.

CONCLUSION

In view of the above, Applicant(s) submit(s) that the application is now in condition for allowance and issue and respectfully request(s) early action to that end. Applicant(s) believe(s) that no additional fees are due. However, should any fees be due, the Commissioner is hereby authorized to charge any fees in connection with this application and to credit any overpayments to Deposit Account No. 14-1447. The undersigned invites the Examiner to contact him/her by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: November 18, 2009

/Shelby J. Walker, Reg. No. 45,192/
Shelby J. Walker, Reg. No. 45,192
Novo Nordisk Inc.
Customer Number 23650
(609) 987-4883

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

NOTICE OF APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Tina Bjeldskov Pedersen, Claude Bonde, and Dorthe Kot Engelund hereby appeal(s) to the Board of Patent Appeals and Interferences from the decision(s) dated June 25, 2009 of the Primary Examiner finally rejecting claims 1-19, 25-28 and 30-44.

Please charge the required fee, currently $540.00, to Novo Nordisk Inc., Deposit Account No. 14-1447. Please charge any additional fees, should they be required, to Deposit Account No. 14-1447.

Respectfully submitted,

Date: November 18, 2009

/Shelby J. Walker, Reg. No. 45,192/
Shelby J. Walker, Reg. No. 45,192
Novo Nordisk Inc.
Customer Number 23650
(609) 987-4883

PTO/SB/25 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) 6683.204-US

In re Application of: Tina Bjeldskov Pedersen et al.

Application No.: 11/435,977

Filed: May 17, 2006

For: Propylene Glycol-Containing Peptide Formulations which are Optimal for Production and for Use in Injection Devices

The owner*, Novo Nordisk A/S, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 11/667,040, filed on May 3, 2007, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent: granted on the pending **reference** application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☑ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☐ The undersigned is an attorney or agent of record. Reg. No. _____

/Shelby J. Walker, Reg. No. 45,192/ — Signature
November 25, 2009 — Date

Shelby J. Walker, Reg. No. 45,192 — Typed or printed name

(609) 987-5800 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

POWER OF ATTORNEY,

REVOCATION OF PREVIOUSLY GRANTED POWER OF ATTORNEY, AND AUTHORIZATION TO MAKE SUBMISSIONS REGARDING OWNERSHIP

Power of Attorney:

Novo Nordisk A/S (hereinafter "Novo Nordisk"), hereby appoints and acknowledges its appointment of the attorneys of the Novo Nordisk Inc. Intellectual Property Department (the latter including the attorneys and agents associated with U.S. Patent and Trademark Office Customer Number 23650) and any successor entities or appointed agents thereof (hereinafter "NNI Attorneys") to act for Novo Nordisk in all proceedings before the U.S. Patent and Trademark Office ("USPTO").

Such proceedings shall include, without limitation, filing, prosecution, withdrawal, maintenance, and abandonment of such U.S. patent applications (and International (PCT) Patent Applications filed with the USPTO), as well as the initiation and handling of appeal, reexamination, reissue, interference, cancellation, correction, or similar proceedings involving U.S. patents and patent applications and the transaction of all other business associated with such patent applications and patents in the U.S. Patent and Trademark Office. By virtue of this appointment, Novo Nordisk authorizes the NNI Attorneys to receive all communications, official actions, and decisions, of the U.S. Patent and Trademark Office and to lodge and withdraw any legal measures deemed fit by the NNI Attorneys with respect to such patents and patent applications.

Revocation of Previously Granted Power of Attorney:

Immediately upon the filing of this document with USPTO in connection with any patent or patent application, all previously granted powers of attorney in connection with the patent or patent application will be revoked.

Authorization To Make Submissions Regarding Ownership:

Novo Nordisk further hereby authorizes and empowers the NNI attorneys to make any appropriate submissions regarding Novo Nordisk's ownership interest in any such patent applications or patents on behalf of Novo Nordisk A/S with the USPTO in accordance with 37 C.F.R. § 3.73(b) (or any substantially similar successor thereof) and having the application number(s) listed thereon.

The individual whose signature and title is supplied below is authorized to grant this power of attorney and authorization to the NNI Attorneys on behalf of Novo Nordisk.

Lars Kellberg

Vice President – Corporate Patents

PTO/SB/96 (01-08)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Tina Bjeldskov Pedersen et al.

Application No./Patent No.: 11/435,977 Filed/Issue Date: May 17, 2006

Entitled: Propylene Glycol-Containing Peptide Formulations which are Optimal for Production and for Use in Injection Devices

Novo Nordisk A/S, a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest
(The extent (by percentage) of its ownership interest is_____ %)

in the patent application/patent identified above by virtue of either:

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 018240, Frame 0830, or for which a copy thereof is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.,* a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Shelby J. Walker, Reg. No. 45,192/	November 25, 2009
Signature	Date
Shelby J. Walker, Reg. No. 45,192	(609) 987-5800
Printed or Typed Name	Telephone Number
IP Counsel	
Title	

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

SUPPLEMENTAL AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Please amend the above-captioned application and consider the remarks herewith as follows:

AMENDMENTS TO THE CLAIMS are reflected in the Listing of Claims which begins on page 2 of this paper.

REMARKS begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS:

The following Listing of Claims replaces all prior versions, and listings, of claims.

LISTING OF CLAIMS

1. (Currently Amended) A pharmaceutical formulation comprising at least one ~~peptide~~ GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.

2. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

3. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

4. (Original) The formulation according to claim 1, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

5. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 9.5.

6. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.

7. (Original) The formulation according to claim 1, wherein the pH of said formulation is about 7.3 to about 8.3.

8. (Original) The formulation according to claim 1, further comprising a preservative.

9. (Original) The formulation according to claim 8, wherein said preservative is present in a concentration from 0.1mg/ml to 20mg/ml.

10. (Cancelled).

11. (Cancelled).

12. (Cancelled).

13. (Original) The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

14. (Original) The formulation according to claim 13, wherein said GLP-1 agonist is a derivative of GLP-1(7-36) or GLP-1(7-37) or a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, where said derivative has a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine.

15. (Original) The formulation according to claim 14, wherein said lipophilic substituent has from 8 to 40 carbon atoms.

16. (Original) The formulation according to claim 15, wherein said spacer is an amino acid.

17. (Original) The formulation according to claim 16, wherein said GLP-1 agonist is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

18. (Original) The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of Gly^8-GLP-1(7-36)-amide, Gly^8-GLP-1(7-37), Val^8-GLP-1(7-36)-amide, Val^8-GLP-1(7-37), Val^8Asp^{22}-GLP-1(7-36)-amide, Val^8Asp^{22}-GLP-1(7-37) , Val^8Glu^{22}-GLP-1(7-36)-amide , Val^8Glu^{22}-GLP-1(7-37), Val^8Lys^{22}-GLP-1(7-36)-amide, Val^8Lys^{22}-GLP-1(7-37), Val^8Arg^{22}-GLP-1(7-36)-amide, Val^8Arg^{22}-GLP-1(7-37), Val^8His^{22}-GLP-1(7-36)-amide, Val^8His^{22}-GLP-1(7-37), Arg34GLP-1(7-37); Arg26,34,Lys36GLP-1(7-36); Arg26GLP-1(7-37); and

Gly8,Arg26,34,Glu37,Lys38GLP-1(7-38) analogues thereof and derivatives of any of these.

19 – 27. (Cancelled).

28. (Currently Amended) A method of preparing a peptide formulation suitable for use in an injection device, said method comprising preparing a formulation containing peptide and propylene glycol and optionally a buffer and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from about 7.0 to about 10.0, and wherein said peptide, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;

b) preparing a second solution by dissolving the peptide in water;

c) mixing the first and second solutions; and

adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

29. (Cancelled).

30. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

31. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

32. (Original) The method according to claim 28, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

33. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 9.5.

34. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.0 to about 8.0.

35. (Original) The method according to claim 28, wherein the pH of said formulation is about 7.2 to about 8.0.

36. (Currently Amended) A method for reducing deposits on production equipment during production of a ~~peptide~~ GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

37. (Original) The method according to claim 36, wherein the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

38. (Original) The method according to claim 36, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

39. (Currently Amended) A method for reducing deposits in the final product during production of a ~~peptide~~ GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

40. (Original) The method according to claim 39, wherein the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or

cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

41. (Original) The method according to claim 39, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, glycerol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

42. (Currently Amended) A method for reducing the clogging of injection devices by a ~~peptide~~ GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

43. (Original) The method according to claim 42, wherein the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

44. (Original) The method according to claim 42, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

REMARKS

Upon entry of the present amendment, claims 1 – 9, 13 – 18, 28 and 30 - 44 are pending. Claims 10 – 12, 19 – 27 and 29 have been cancelled. Claims 1, 28, 36, 39 and 42 have been amended to correct a grammatical error. The present amendment adds no new matter.

THE NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

The Examiner has made the following provisional rejections on the grounds of nonstatutory obviousness-type double patenting: 1) Claims 1-18 and 25-44 are rejected as being unpatentable over claims 1-63 of copending US Patent Application No. 11/667,040; and 2) Claims 1-12 and 28-44 are rejected as being unpatentable over claims 1, 3-11, 19-21, 29 and 48-54 of copending US Patent Application No. 11/244,497.

Applicants have filed all necessary Terminal Disclaimers herewith. Accordingly, Applicants believe that the present rejection is now moot.

CONCLUSION

In view of the above, Applicant(s) submit(s) that the application is now in condition for allowance and issue and respectfully request(s) early action to that end. Applicant(s) believe(s) that no additional fees are due. However, should any fees be due, the Commissioner is hereby authorized to charge any fees in connection with this application and to credit any overpayments to Deposit Account No. 14-1447. The undersigned invites the Examiner to contact him/her by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: November 25, 2009

/Shelby J. Walker, Reg. No. 45,192/
Shelby J. Walker, Reg. No. 45,192
Novo Nordisk Inc.
Customer Number 23650
(609) 987-4883

PTO/SB/25 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) 6683.204-US

In re Application of: Tina Bjeldskov Pedersen et al.

Application No.: 11/435,977

Filed: May 17, 2006

For: Propylene Glycol-Containing Peptide Formulations which are Optimal for Production and for Use in Injection Devices

The owner*, Novo Nordisk A/S, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 11/244,497, filed on October 3, 2005, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent: granted on the pending **reference** application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☑ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☐ The undersigned is an attorney or agent of record. Reg. No. _____

/Shelby J. Walker, Reg. No. 45,192/ — Signature
November 25, 2009 — Date

Shelby J. Walker, Reg. No. 45,192 — Typed or printed name

(609) 987-5800 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/435,977	PEDERSEN ET AL.	

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TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 11/25/09	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Janice Ford two terminals approved

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

23650 7590 12/03/2009

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
12/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
KSHL@novonordisk.com
KISW@novonordisk.com

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	11/435,977	PEDERSEN ET AL.	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

All Participants:

(1) *CHRISTINA BRADLEY*.

(2) *Shelby Walker*.

Status of Application: _____

(3) _____.

(4) _____.

Date of Interview: *24 November 2009*

Time: _____

Type of Interview:
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No
If Yes, provide a brief description: .

Part I.

Rejection(s) discussed:

Claims discussed:

Prior art documents discussed:

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:

The Examiner contacted Applicant to ask if the amendment to claim 1 to include "a disodium phosphate dehydrate buffer" was intended to be "a disodium dihydrate buffer," the former being new matter and the latter being supported in the specification. Ms. Walker confirmed that the dihydrate was intended and that dehydrate is a typographical error. The Examiner indicated that amending the claim to dihydrate would overcome the pending rejection under 35 U.S.C. § 102(e) but that the non-statutory double patenting rejections would be maintained. Applicant agreed to file a supplemental amendment to correct the claims and cancel withdrawn claims and to file terminal disclaimers. The Examiner agreed that all other claim amendments would be entered when the supplemental amendment is filed.

Part III.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

(Applicant/Applicant's Representative Signature – if appropriate)

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

SUPPLEMENTAL AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Please amend the above-captioned application and consider the remarks herewith as follows:

AMENDMENTS TO THE CLAIMS are reflected in the Listing of Claims which begins on page 2 of this paper.

REMARKS begin on page 7 of this paper.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

23650 7590 12/16/2009

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 12/16/2009

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	03/16/2010

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23650 7590 12/16/2009

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	03/16/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
BRADLEY, CHRISTINA	1654	514-002000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

23650 7590 12/16/2009

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 12/16/2009

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 250 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 250 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	11/435,977	PEDERSEN ET AL.	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the after-final amendment filed 11/25/2009*.

2. ☒ The allowed claim(s) is/are *1-9,13-18,28 and 30-44*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Anish Gupta/
Primary Examiner, Art Unit 1654

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Shelby Walker on December 2, 2009.

The application has been amended as follows:

In claim 18, lines 5-6, delete "Arg34GLP- 1(7-37); Arg26,34,Lys36GLP- 1 (7-36); Arg26GLP-l(7-37); and Gly8,Arg26,34,Glu37,Lys38GLP- 1(7-38) analogues thereof and derivatives of any of these." and insert --Arg^{34}GLP- 1(7-37), $Arg^{26,34}Lys^{36}$GLP- 1 (7-36), Arg^{26}GLP-l(7-37), and $Gly^{8}Arg^{26,34}Glu^{37}Lys^{38}$GLP- 1(7-38) and derivatives of any of these." therefor.

28. (Currently Amended) A method of preparing a GLP-1 agonist~~peptide~~ formulation suitable for use in an injection device, said method comprising preparing a formulation containing a GLP-1 agonist,~~peptide and~~ propylene glycol, a disodium phosphate dihydrate buffer, ~~and optionally a buffer~~ and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from about 7.0 to about 10.0, and wherein said GLP-1 agonist~~peptide~~, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;

b) preparing a second solution by dissolving the GLP-1 agonist~~peptide~~ in water;

c) mixing the first and second solutions; and

adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

2. The following is an examiner's statement of reasons for allowance: The rejection of claims 1-19, 22-28 and 30-44 under 35 U.S.C. 102(e) as being anticipated by Knudsen et al. (US 2006/0287221) is overcome by the amendment filed 11/25/2009. Knudsen et al. teaches phosphate buffer which is generic to the species disodium phosphate dihydrate buffer now claimed. Therefore, the claims are not anticipated by Knudsen et al. Furthermore, the reference is disqualified as prior art under 35 U.S.C. 103(c). The non-statutory double patenting rejections over 11/667,040 and 11/244,497 are overcome by the terminal disclaimers filed 11/25/2009. The non-statutory double patenting rejection over 11/417,562 is moot because the case is now abandoned.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 8:30 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654/

cmb

Receipt date: 07/17/2006

11435977 - GAU: 1654

FORM PTO-1449 (Rev. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	Atty. Docket No. 6683.204-US	Serial No. 11/435,977
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	Applicant Pedersen et al.	
	Filing Date May 17, 2006	Group 1646

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		2002/0151467	12/21/00	Leung, F.K.			
		5206219	11/25/91	Applied Analytical Industries, INC			

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		2005/046716	~~11/12/04~~	5/26/2005 WO				
		93/23010	~~05/07/92~~	11/25/1993 WO				
		95/13825	~~10/24/94~~	5/26/1995 WO				
		99/16417	~~10/01/97~~	4/8/1999 WO				
		03/013589	~~05/20/02~~	2/20/2003 WO				
		1424077	05/20/02	EP				
		95/22560	02/21/95	WO				
		95/05848	~~08/23/94~~	3/2/1995 WO				
		02/067989	01/08/02	WO				
		92/19260	~~05/07/91~~	11/12/1992 WO				

1/15 T.T.

1/15 T.T.

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

			Singh, S et al - Aaps Pharmscitech - 2003 - Vol. 4 - Part 3-Pgs.334-342

EXAMINER /Christina Bradley/ DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Receipt date: 07/17/2006 11435977 - GAU: 1654

FORM PTO-1449 (Rev. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	Atty. Docket No. 6683.204-US	Serial No. 11/435,977
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	Applicant Pedersen et al.	
	Filing Date May 17, 2006	Group 1646

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		2002/0151467	~~12/31/00~~	Leung, F.K.			10/17/2002
		5206219	11/25/91	Applied Analytical Industries, INC			

1/19 J.T.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		2005/046716	11/12/04	WO				
		93/23010	05/07/92	WO				
		95/13825	10/24/94	WO				
		99/16417	10/01/97	WO				
		03/013589	05/20/02	WO				
		1424077	05/20/02	EP				
		95/22560	02/21/95	WO				
		95/05848	08/23/94	WO				
		02/067989	01/08/02	WO				
		92/19260	05/07/91	WO				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

			Singh, S et al - Aaps Pharmscitech - 2003 - Vol. 4 - Part 3-Pgs.334-342

EXAMINER /Christina Bradley/	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	11/435,977	Filing Date	2006-05-17	Docket Number (if applicable)	6683.204-US	Art Unit	1654
First Named Inventor	Pedersen			Examiner Name	Bradley, Christina		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☑ Enclosed

- ☐ Amendment/Reply
- ☑ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☑ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 141447

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

◉ Patent Practitioner Signature

☐ Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	/Shelby J. Walker, Reg. No. 45,192/	Date (YYYY-MM-DD)	2010-03-15
Name	Shelby J. Walker, Reg. No. 45,192	Registration Number	45192

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Conf. No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In accordance with Applicants' duty of disclosure under 37 C.F.R. § 1.56, and supplemental to the Information Disclosure Statement filed January 11, 2007, Applicants hereby submit the following Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98, and in conformance with MPEP 609 and 37 C.F.R. § 1.98(d).

Applicants hereby make of record the documents cited in the following commonly owned U.S. Application which are not already of record in the present application:

- U.S. App. No. 12/184,531, filed August 1, 2008 by Juul-Mortensen et al. (published as 2008/0318865 on December 25, 2008)

Applicant(s) submit herewith the Office Action(s) listed on the accompanying Form(s) PTO-1449. The Examiner is encouraged to review any responses in the herein mentioned applications, and Applicant(s) assume(s) that due to the ease of review on PAIR by the Examiner, these responses need not be submitted. Since prosecution may be ongoing in the herein mentioned application(s), Applicant(s) assume(s) that the Examiner will continue to evaluate the application(s) as needed.

The Examiner is requested to initial the attached Form PTO-1449, and to return the initialed copy with the next communication from the U.S. Patent and Trademark Office.

Applicants hereby submit one Form PTO-1449 sheet listing the above-noted documents for consideration by the Examiner in accordance with 37 C.F.R. §§ 1.56, 1.97, and 1.98:

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	1	Atty. Docket No.	6683.204-US

U.S. PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Issue/Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T
		Non-Final Office Action mailed December 9, 2009 in U.S. Application No. 12/184,531 filed August 1, 2008 by Mortensen *et al.*	

EXAMINER SIGNATURE		DATE CONSIDERED	

REMARKS

Pursuant to 37 C.F.R. § 1.98 copies of the U.S. patent documents (patents, application publications, and applications) are not being submitted herewith. Of course, should any of the documents not be readily available to the Examiner, the Examiner is requested to contact the undersigned and additional copies will be submitted.

Applicants note that Copyrighted material submitted with this Information Disclosure Statement may be delivered to the Government under license from the Copyright Clearance Center, Inc., or other rights holders – no further reproduction of such works is permitted.

Inclusion of any reference is not intended to constitute an admission that the reference is "prior art" unless it is specifically designated as such.

This Information Disclosure Statement is being filed **within** three months of the filing date of a national application or date of entry into the national stage of an international application or **before** the mailing date of a first Office action on the merits, or **before** the mailing date of a first Office action after the filing of a request for continued examination as per the requirements of 37 CFR § 1.97(b). Therefore, no fee is due. However, please charge any fees should they be required, to Novo Nordisk Inc. Deposit Account No. 14-1447.

Applicants respectfully request that any references or other information listed above be made of record in this patent application. The Examiner is invited to call the undersigned if there are any questions concerning this submission or application.

Respectfully submitted,

Date: March 16, 2010

/Shelby J. Walker, Reg. No. 45,192/

Shelby J. Walker, Reg. No. 45,192
Novo Nordisk Inc.
Customer Number 23650
(609) 987-4883

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23650 7590 04/06/2010

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 04/06/2010

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	07/06/2010

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23650 7590 04/06/2010

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	07/06/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
BRADLEY, CHRISTINA	1654	514-002000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

23650 7590 04/06/2010

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 04/06/2010

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 250 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 250 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	11/435,977	PEDERSEN ET AL.	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the RCE filed 3/16/2010*.

2. ☒ The allowed claim(s) is/are *1-9,13-18,28 and 30-44*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 3/16/2010
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 03/16/2010 has been entered.

2. The information disclosure statement (IDS) submitted on 03/16/2010 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

3. Claims 1-9, 13-18, 28 and 30-44 are allowed as they appear in the Examiner's Amendment mailed 12/16/2009 and for the reasons presented in that Office action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 8:30 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	1	Atty. Docket No.	6683.204-US

U.S. PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Issue/Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T
/C.B./		Non-Final Office Action mailed December 9, 2009 in U.S. Application No. 12/184,531 filed August 1, 2008 by Mortensen *et al.*	

EXAMINER SIGNATURE	/Christina Bradley/	DATE CONSIDERED	03/26/2010

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	11/435,977	Filing Date	2006-05-17	Docket Number (if applicable)	6683.204-US	Art Unit	1654
First Named Inventor	Pedersen			Examiner Name	Bradley, Christina		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☐ Amendment/Reply

☒ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 141447

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Shelby J. Walker, Reg. No. 45,192/	Date (YYYY-MM-DD)	2010-06-22
Name	Shelby J. Walker	Registration Number	45192

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	11/435,977	Filing Date	2006-05-17	Docket Number (if applicable)	6683.204-US	Art Unit	1654
First Named Inventor	Pedersen			Examiner Name	Bradley, Christina		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 141447

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Shelby J. Walker, Reg. No. 45,192/	Date (YYYY-MM-DD)	2010-06-22
Name	Shelby J. Walker	Registration Number	45192

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant(s) hereby submit(s) three (3) sheet(s) listing references and other information for consideration by the Examiner in accordance with 37 C.F.R. 1.56, 1.97, and 1.98:

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	3	Atty. Docket No.	6683.204-US

U.S. PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code (if known)	Issue/Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
		5,272,135	12-21-93	Takruri	
		5,705,483	01-06-98	Galloway	
		6,184,201	02-06-01	Drucker et al.	
		6,268,343	07-31-01	Knudsen et al.	
		6,274,553	08-14-01	Furuya	
		6,586,399	07-01-03	Drucker et al.	
		2001/0014666	08-16-01	Hermeling et al.	
		2001/0027180	10-04-01	Isaacs	
		2003/0060412	03-27-03	Prouty et al.	
		2003/0069182	04-10-03	Rinella	
		2003/0158101	08-21-03	Drucker	
		2003/0207802	11-06-03	DeFelippis	
		2003/0220243	11-27-03	Glaesner et al.	
		2004/0248782	12-09-04	Bridon et al.	

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code (if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T
		WO 96/20005	07-04-96	Novo Nordisk A/S		
		WO 98/08871	03-05-98	Novo Nordisk A/S		
		WO 98/31386 (corresponds to US 6,274,553 above)	07-23-98	Japan Energy Corp.		
		WO 99/29336	06-17-99	Eli Lilly & Co.		
		WO 99/30731	06-24-99	Eli Lilly & Co.		
		WO 99/43341	09-02-99	Novo Nordisk A/S		
		WO 99/43708	09-22-99	Novo Nordisk A/S		
		WO 00/15224	03-23-00	Eli Lilly & Co.		
		WO 00/37098	06-29-00	Eli Lilly & Co.		
		WO 00/41546	07-20-00	Amylin Pharmaceuticals		
		WO 00/55119	09-21-00	Novo Nordisk A/S		
		WO 01/43762	06-2101	Eli Lilly & Co.		
		WO 01/49314	07-12-01	NPS Allelix Corp.		

EXAMINER SIGNATURE		DATE CONSIDERED	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	3	Atty. Docket No.	6683.204-US

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EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T
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		JP 2001-525371 (corresponds to WO 99/29336 above)	12-11-01	Eli Lilly & Co.		
		JP 2002-508332 (corresponds to WO 99/30731 above)	03-19-02	Eli Lilly & Co.		
		JP 2002-532557 (corresponds to WO 00/37098 above)	10-02-02	Eli Lilly & Co.		
		RU 2180218 (corresponds to WO 98/31386 above)	03-10-02	Japan Energy Corp.		
		WO 01/77141	10-18-01	Novo Nordisk A/S		
		WO 02/47715	06-20-02	Eli Lilly & Co.		
		WO 02/48183	06-20-02	Eli Lilly & Co.		
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		WO 03/035099	05-01-03	Eli Lilly & Co.		
		WO 2004/029076	04-08-04	Novo Nordisk A/S		
		WO 2005/000222	01-06-05	Amylin Pharmaceuticals		
		WO 2006/025882	03-09-06	UAB Research		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
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				Examiner Name:	Bradley, Christina
Sheet	3	of	3	Atty. Docket No.	6683.204-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T
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Except for US patent documents, a copy of each listed reference is enclosed or submitted herewith.

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Inclusion of any reference is not intended to constitute an admission that the reference is "prior art" unless it is specifically designated as such.

This Information Disclosure Statement is being filed **within** three months of the filing date of a national application or date of entry into the national stage of an international application or **before** the mailing date of a first Office action on the merits, or **before** the mailing date of a first Office action after the filing of a request for continued examination as per the requirements of 37 CFR § 1.97(b). Therefore, no fee is due. However, please charge any fees should they be required, to Novo Nordisk Inc. Deposit Account No. 14-1447.

Applicant(s) respectfully request(s) that any references or other information listed above be made of record in this patent application. The Examiner is invited to call the undersigned if there are any questions concerning this submission or application.

Respectfully submitted,

Date: June 25, 2010

/Shelby J. Walker, Reg. No. 45,192/
Shelby J. Walker, Reg. No. 45,192
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Conf. No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450, AMENDMENT
Alexandria, VA 22313-1450

Dear Sir:

In accordance with Applicants' duty of disclosure under 37 C.F.R. § 1.56, and supplemental to the Information Disclosure Statement filed JUNE 25, 2010, Applicants hereby submit the following Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98, and in conformance with MPEP 609 and 37 C.F.R. § 1.98(d).

Applicants hereby make of record the following commonly owned U.S. Application(s) which may not already be of record in the present application,

- U.S. App. No. 10/185,923, filed JUNE 27, 2002, Inventors: FLINK et al. (Attorney Docket No. 6358.500-US) (Abandoned);
- U.S. App. No. 11/786,095, filed APRIL 11,2007, Inventors: FLINK et al. (Attorney Docket No. 6358.510-US) (Abandoned);
- U.S. App. No. 12/343,722, filed DECEMBER 24, 2008, Inventors: FLINK et al. (Attorney Docket No. 6358.520-US) (Abandoned);
- U.S. App. No. 12/785,861, Filed on MAY 24, 2010, by FLINK et al. (Attorney Docket No. 6358.530-US);

- U.S. App. No. 11/290,635, Filed NOVEMBER 30, 2005, by JUUL-MORTENSEN (Attorney Docket No. 6689.204-US)(Abandoned);
- U.S. App. No. 12/184,531, Filed AUGUST 1, 2008, by JUUL-MORTENSEN (Attorney Docket No. 6689.214-US);
- U.S. App. No. 11/290,634, Filed NOVEMBER 30, 2005, by JUUL-MORTENSEN et al. (Attorney Docket No. 6702.204-US) (ISSUED);
- U.S. App. No. 12/612,888, Filed NOVEMBER 5, 2009, by JUUL-MORTENSEN et al. (Attorney Docket No. 6702.214-US)
- U.S. App. No. 11/365,274, Filed MARCH 1, 2006, by SCHLEIN et al. (Attorney Docket No. 6711.204-US) (Abandoned);
- U.S. App. No. 12/752,634, Filed APRIL 1, 2010, by SCLEIN et al. (Attorney Docket No. 6711.214-US);
- U.S. App. No. 11/667,040, Filed MAY 3, 2007, by LUDVIGSEN ET AL. (Attorney Docket No. 7001.504-US) (Abandoned);
- U.S. App. No. 12/643,330, Filed DECEMBER 21, 2009, by LUDVIGSEN ET AL.. (Attorney Docket No. 7001.514-US)

Applicants may also submit herewith Office Actions and, *inter alia*, any documents cited therein, and these documents are listed on the accompanying Forms PTO-1449.

The Examiner is encouraged to review any associated Applicant responses in the above mentioned applications, and Applicants assume that due to the ease of review on PAIR by the Examiner, these responses need not be submitted/listed. Since prosecution may be ongoing in the herein mentioned applications, Applicants assume that the Examiner will continue to evaluate the applications as needed.

The Examiner is requested to consider the attached Form PTO-1449, and to return the initialed and signed copy with the next communication from the U.S. Patent and Trademark Office.

Applicants hereby submit 5 Forms PTO-1449 sheet for consideration by the Examiner in accordance with 37 C.F.R. §§ 1.56, 1.97, and 1.98:

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	5	Atty. Docket No.	6683.204-US

U.S. PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Issue/Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
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EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T
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EXAMINER SIGNATURE		DATE CONSIDERED	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
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				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	5	Atty. Docket No.	6683.204-US

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T
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				Filing Date	May 17, 2006
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				Art Unit	1654
				Examiner Name:	Bradley, Christina
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT					
				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	4	of	5	Atty. Docket No.	6683.204-US

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		FINAL OFFICE ACTION IN 12/343,722, FILED DECEMBER 24, 2008, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.520-US) SENT FEBRUARY 18, 2009	
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EXAMINER SIGNATURE		DATE CONSIDERED	

REMARKS

Pursuant to 37 C.F.R. § 1.98 copies of the U.S. patent documents (patents, application publications, and applications are not being submitted herewith. Of course, should any of the documents not be readily available to the Examiner, the Examiner is requested to contact the undersigned and additional copies will be submitted.

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Applicants respectfully request that any references or other information listed above be made of record in this patent application. The Examiner is invited to call the undersigned if there are any questions concerning this submission or application.

Respectfully submitted,

Date: July 26, 2010

____/ Teresa Chen, Reg. No. 55,352/_____
Teresa Chen, Reg. No. 55,352
Novo Nordisk Inc.
Customer Number 23650
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INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER
BRADLEY, CHRISTINA

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/14/2011

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	06/14/2011

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

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If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23650 7590 03/14/2011

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	06/14/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
BRADLEY, CHRISTINA	1654	514-002000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

23650 7590 03/14/2011

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 03/14/2011

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 390 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 390 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

Notice of Allowability	Application No.	Applicant(s)
	11/435,977	PEDERSEN ET AL.
	Examiner	Art Unit
	CHRISTINA BRADLEY	1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the RCE filed 06/25/2010*.

2. ☒ The allowed claim(s) is/are *1-9,13-18,28 and 30-44*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)	5. ☐ Notice of Informal Patent Application
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)	6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date See Continuation Sheet	7. ☐ Examiner's Amendment/Comment
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material	8. ☒ Examiner's Statement of Reasons for Allowance
	9. ☐ Other _____.
/Christina Marchetti Bradley/ Primary Examiner, Art Unit 1654	

Continuation of Attachment(s) 3. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 07/28/2010, 06/25/2010.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under Ex Parte Quayle, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 06/25/2010 has been entered.

2. The information disclosure statement (IDS) submitted on 07/28/2010 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

3. Numerous NPL citations on the information disclosure statement filed 06/25/2010 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because they are missing titles and/or dates. All references on the IDS filed 06/25/2010 have been considered except for the references that are lined-through. These references have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

4. Claims 1-9, 13-18, 28 and 30-44 are allowed as they appear in the Examiner's Amendment mailed 12/16/2009 and for the reasons presented in that Office action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 8:30 A.M. to 4:30 P.M.

6. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

7. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christina Marchetti Bradley/
Primary Examiner, Art Unit 1654

cmb

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	3	Atty. Docket No.	6683.204-US

U.S. PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Issue/Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
		5,272,135	12-21-93	Takruri	
		5,705,483	01-06-98	Galloway	
		6,184,201	02-06-01	Drucker et al.	
		6,268,343	07-31-01	Knudsen et al.	
		6,274,553	08-14-01	Furuya	
		6,586,399	07-01-03	Drucker et al.	
		2001/0014666	08-16-01	Hermeling et al.	
		2001/0027180	10-04-01	Isaacs	
		2003/0060412	03-27-03	Prouty et al.	
		2003/0069182	04-10-03	Rinella	
		2003/0158101	08-21-03	Drucker	
		2003/0207802	11-06-03	DeFelippis	
		2003/0220243	11-27-03	Glaesner et al.	
		2004/0248782	12-09-04	Bridon et al.	

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T
		WO 96/20005	07-04-96	Novo Nordisk A/S		
		WO 98/08871	03-05-98	Novo Nordisk A/S		
		WO 98/31386 (corresponds to US 6,274,553 above)	07-23-98	Japan Energy Corp.		
		WO 99/29336	06-17-99	Eli Lilly & Co.		
		WO 99/30731	06-24-99	Eli Lilly & Co.		
		WO 99/43341	09-02-99	Novo Nordisk A/S		
		WO 99/43708	09-22-99	Novo Nordisk A/S		
		WO 00/15224	03-23-00	Eli Lilly & Co.		
		WO 00/37098	06-29-00	Eli Lilly & Co.		
		WO 00/41546	07-20-00	Amylin Pharmaceuticals		
		WO 00/55119	09-21-00	Novo Nordisk A/S		
		WO 01/43762	06-2101	Eli Lilly & Co.		
		WO 01/49314	07-12-01	NPS Allelix Corp.		

EXAMINER SIGNATURE		DATE CONSIDERED	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	3	Atty. Docket No.	6683.204-US

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T
		EP 708179	04-24-96	Eli Lilly & Co.		
		JP 2001-525371 (corresponds to WO 99/29336 above)	12-11-01	Eli Lilly & Co.		
		JP 2002-508332 (corresponds to WO 99/30731 above)	03-19-02	Eli Lilly & Co.		
		JP 2002-532557 (corresponds to WO 00/37098 above)	10-02-02	Eli Lilly & Co.		
		RU 2180218 (corresponds to WO 98/31386 above)	03-10-02	Japan Energy Corp.		
		WO 01/77141	10-18-01	Novo Nordisk A/S		
		WO 02/47715	06-20-02	Eli Lilly & Co.		
		WO 02/48183	06-20-02	Eli Lilly & Co.		
		WO 03/002136	04-09-03	Novo Nordisk A/S		
		WO 03/020201	03-13-03	Eli Lilly & Co.		
		WO 03/035099	05-01-03	Eli Lilly & Co.		
		WO 2004/029076	04-08-04	Novo Nordisk A/S		
		WO 2005/000222	01-06-05	Amylin Pharmaceuticals		
		WO 2006/025882	03-09-06	UAB Research		

EXAMINER SIGNATURE	/Christina Bradley/	DATE CONSIDERED	03/03/2011

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	3	of	3	Atty. Docket No.	6683.204-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T
		BERENDSEN, H. J. C., Science, 1998, Vol. 282, pages 642-643	
		BLUNDELL, T.L., Lefébvre P.J. (Ed), 1983, Vol. 66, pages 37-55	
		CHOU, J. Z. ET AL., Journal of Pharmaceutical Sciences, 1997, Vol. 86, No. 7, pages 768-773	
		COPE, WWW.COPEWITHCYTOKINES.DE/COPE.CGI?KEY=GLP%2D1, GLP-1	
		COPE, HTTP:WWW.COPEWITHCYTOKINES.DE/COPE.CGI?, CYTOKINES & CELLS ONLINE PATHFINDER ENCYCLOPEDIA: INSULINOTROPIN	
		Council of Europe., Strasbourg, European Pharmacopoeia, 2007, Vol. 1, page 730	
		GOOD, N. E., www.FERMANTES.COM	
		GOOD, N. E. ET AL., Biochemistry, 1966, Vol. 5, No. 2, pages 467-477	
		LARSEN, P. J. ET AL., Diabetes 2001, Vol. 50, pages 2530-2539	
		MALENDOWICH ET AL., Journal of Molecular Medicine, 2002, Vol. 10, No. 3, pages 327-331	
		MESSER, W. S., Vasopressin and Oxytocin, 2000	
		QI, H. ET AL., PDA Journal of Pharmaceutical Science & Technology, 1995, Vol. 49, No. 6, pages 289-293	
		RUDINGER, J., Peptide Hormones, 1976, pages 1-7	
		SENDEROFF, R. I. ET AL., J. Pharm. Sci., 1998, Vol. 87, Part 2, pages 183-189	
		SIGMA, Custom Peptide Synthesis, 2004, pages 1-2, http://www.SIGMA-GENOSYS.COM/PEPTIDE_DESIGN.ASP	
		SMILEK, D. E. ET AL., Proceedings of the National Academy of Sciences of USA, 1991, Vol. 88, pages 9033-9037	
		STAMPER, G. F. ET AL., Drug Development and Industrial Pharmaceuticals, 1995, Vol. 21, No. 13, pages 1503-1511	
		VOET, D. ET AL., Biochemistry, 1995, 2nd Edition, pages 235-241	

EXAMINER SIGNATURE	/Christina Bradley/	DATE CONSIDERED	03/03/2011

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

Except for US patent documents, a copy of each listed reference is enclosed or submitted herewith.

Copyrighted material submitted with this Information Disclosure Statement may be delivered to the Government under license from the Copyright Clearance Center, Inc., or other rights holders – no further reproduction of such works is permitted.

Inclusion of any reference is not intended to constitute an admission that the reference is "prior art" unless it is specifically designated as such.

This Information Disclosure Statement is being filed **within** three months of the filing date of a national application or date of entry into the national stage of an international application or **before** the mailing date of a first Office action on the merits, or **before** the mailing date of a first Office action after the filing of a request for continued examination as per the requirements of 37 CFR § 1.97(b). Therefore, no fee is due. However, please charge any fees should they be required, to Novo Nordisk Inc. Deposit Account No. 14-1447.

Applicant(s) respectfully request(s) that any references or other information listed above be made of record in this patent application. The Examiner is invited to call the undersigned if there are any questions concerning this submission or application.

Respectfully submitted,

Date: June 25, 2010

/Shelby J. Walker, Reg. No. 45,192/
Shelby J. Walker, Reg. No. 45,192
Novo Nordisk Inc.
Customer Number 23650
(609) 987-4883

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	5	Atty. Docket No.	6683.204-US

U.S. PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Issue/Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
		4468346	Aug-1984	PAUL ET AL.	
		5455331	10/3/1995	PEARCE	
		5652216	7/29/1997	KORNFELT ET	
		6133229	Oct-2000	GIBSON ET AL.	
		6284727	Sep-2001	KIM ET AL.	
		6380357	8/16/2001	HERMELING	
		6384016	5/7/2002	KAARSHOLM	
		6444788	Sep-2002	STABY, ARNE	
		6844321	1/1/2005	ARENTSEN,	
		7022674	Apr-2006	DEFELIPPIS ET	
		7049284	5/23/2006	DRUCKER ET	
		7056886	6/6/2006	ISSACS	
		7238663	Jul-2007	DEFELIPPIS ET	
		20030119734	Jun-2003	FLINK ET AL.	
		20030220255	11/27/200	KNUDSEN ET	
		20040248782	12/9/2004	BRIDON ET AL.	

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T
		WO0152937	7/26/2001	MINIMED INC.		
		EP1344533	9/17/2003	NATIMMUNE A/S		
		EP1396499	3/10/2004	ELI LILLY & CO.		
		EP747390	12/11/1996	ELI LILLY & CO.		
		WO9510605	4/20/1995	THE UNIVERSITY OF LEEDS INNOVATIONS LTD.		
		EP0431679	11/28/1990	MERCK		

EXAMINER SIGNATURE	/Christina Bradley/	DATE CONSIDERED	03/03/2011

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	5	Atty. Docket No.	6683.204-US

FOREIGN PATENT DOCUMENTS

		EP0438767	12/22/1990	BASF		
		EP0926159	6/30/1999	ELI LILLY		
		EP1329462	10/24/2001	THE JURIDICAL FOUNDATION		
		EP699687	8/30/1995	THE GREEN CROSS CORP.		
		JP10101696	4/21/1998	JAPAN FOUND. FOR CANCER RESEARCH		T
		PA200101010	6/28/2001	NOVO NORDISK		
		WO0155213	8/2/2001	ELI LILLY		
		WO0248183	6/20/2002	ELI LILLY		
		WO9000200	1/11/1990	GENEX		
		WO9638469	12/5/1996	NOVO NORDISK		
		WO9921889	MAY-1999	GENENTECH		
		WO9943707	9/2/1999	NOVO NORDISK		
		WO2004105781	12/9/2004	NOVO NORDISK		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T
		BAILEY ET AL. THE KINETICS OF ENZYME-CATALYSED REACTIONS Biochemical Engineering Fundamentals, 2nd Ed., pp. 129-148 (1986)	
		ENTRY FOR GLYCERIN IN DRUGS.COM (WWW.DRUGS.COM/PPA/GLYCERIN-GLYCEROL.HTML), PRINTED 08/04/2009	
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EXAMINER SIGNATURE		DATE CONSIDERED	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	3	of	5	Atty. Docket No.	6683.204-US

NON PATENT LITERATURE DOCUMENTS

		SKOVGAARD ET AL., "USING EVOLUTIONARY INFORMATION AND ANCESTRAL SEQUENCES TO UNDERSTAND THE SEQUENCE-FUNCTION RELATIONSHIP IN GLP-1 AGONISTS," J. MOL. BIO., 2006, VOL. 363, PAGES 977-988	
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		NON-FINAL OFFICE ACTION IN 10/185,923, FILED JUNE 27, 2002, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.500-US) SENT MARCH 10, 2006	
		NON-FINAL OFFICE ACTION IN 10/185,923, FILED JUNE 27, 2002, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.500-US) SENT OCTOBER 9, 2007	
		NON-FINAL OFFICE ACTION IN 11/786,095, FILED APRIL 11,2007, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.510-US) SENT FEBRUARY 24, 2009	
		NON-FINAL OFFICE ACTION IN 12/343,722, FILED DECEMBER 24, 2008, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.520-US) SENT MAY 22, 2009	
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		NON-FINAL OFFICE ACTION IN 11/220,266, FILED SEPTEMBER 6, 2005, INVENTORS: MARKUSSEN ET AL. (ATTORNEY DOCKET NO. 6555.210-US) SENT SEPTEMBER 14, 2006	
		NON-FINAL OFFICE ACTION IN 11/220,266, FILED SEPTEMBER 6, 2005, INVENTORS: MARKUSSEN ET AL. (ATTORNEY DOCKET NO. 6555.210-US) SENT FEBRUARY 11, 2008	
		NON-FINAL OFFICE ACTION IN 11/220,266, FILED SEPTEMBER 6, 2005, INVENTORS: MARKUSSEN ET AL. (ATTORNEY DOCKET NO. 6555.210-US) SENT OCTOBER 1, 2007	

EXAMINER SIGNATURE		DATE CONSIDERED	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	4	of	5	Atty. Docket No.	6683.204-US

NON PATENT LITERATURE DOCUMENTS

		NON-FINAL OFFICE ACTION IN 11/290,634, FILED NOVEMBER 30, 2005, INVENTORS: JUUL-MORTENSEN ET AL. (ATTORNEY DOCKET NO. 6702.204-US) SENT JUNE 30, 2008	
		NON-FINAL OFFICE ACTION IN 11/290,634, FILED NOVEMBER 30, 2005, INVENTORS: JUUL-MORTENSEN ET AL. (ATTORNEY DOCKET NO. 6702.204-US) SENT NOVEMBER 9, 2007	
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		NON-FINAL OFFICE ACTION IN 11/365,274, FILED MARCH 1, 2006, INVENTORS: SCHLEIN ET AL. (ATTORNEY DOCKET NO. 6711.204-US) SENT FEBRUARY 5, 2007	
		NON-FINAL OFFICE ACTION IN 11/365,274, FILED MARCH 1, 2006, INVENTORS: SCHLEIN ET AL. (ATTORNEY DOCKET NO. 6711.204-US) SENT JANUARY 28, 2009	
		FINAL OFFICE ACTION IN 10/185,923, FILED JUNE 27, 2002, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.500-US) SENT DECEMBER 12, 2006	
		FINAL OFFICE ACTION IN 10/185,923, FILED JUNE 27, 2002, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.500-US) SENT JUNE 14, 2005	
		FINAL OFFICE ACTION IN 10/185,923, FILED JUNE27, 2002, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.500-US) SENT JUNE 30, 2008	
		FINAL OFFICE ACTION IN 11/290,635, FILED , INVENTORS: JUUL-MORTENSEN ET AL. (ATTORNEY DOCKET NO. 6689.204-US) SENT SEPTEMBER 5, 2007	

EXAMINER SIGNATURE		DATE CONSIDERED	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

Attorney Docket No.: 6683.204-US U.S. Application No. 11/435,977

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	5	of	5	Atty. Docket No.	6683.204-US

NON PATENT LITERATURE DOCUMENTS

		FINAL OFFICE ACTION IN 11/290,635, FILED NOVEMBER 30, 2005, INVENTORS: JUUL-MORTENSEN ET AL. (ATTORNEY DOCKET NO. 6689.204-US) SENT SEPTEMBER 5, 2007	
		FINAL OFFICE ACTION IN 11/365,274, FILED MARCH 1, 2006, INVENTORS: SCHLEIN ET AL. (ATTORNEY DOCKET NO. 6711.204-US) SENT APRIL 4, 2008	
		FINAL OFFICE ACTION IN 11/365,274, FILED MARCH 1, 2006, INVENTORS: SCHLEIN ET AL. (ATTORNEY DOCKET NO. 6711.204-US) SENT AUGUST 12, 2009	
		FINAL OFFICE ACTION IN 11/786,095, FILED APRIL 11,2007, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.510-US) SENT NOVEMBER 24, 2009	
		FINAL OFFICE ACTION IN 12/343,722, FILED DECEMBER 24, 2008, INVENTORS: FLINK ET AL. (ATTORNEY DOCKET NO. 6358.520-US) SENT FEBRUARY 18, 2009	
		BRITTAIN, HARRY G., BUFFERS, BUFFERING AGENTS, AND IONIC EQUILIBRIA, ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY, PG. 385, 2007	

EXAMINER SIGNATURE	/Christina Bradley/	DATE CONSIDERED	03/03/2011

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	11/435,977	Filing Date	2006-05-17	Docket Number (if applicable)	6683.204-US	Art Unit	1654
First Named Inventor	Pedersen			Examiner Name	Bradley, Christina		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 141447

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Michael J. Brignati, Reg. No. 60.890/	Date (YYYY-MM-DD)	2011-06-10
Name	Michael J. Brignati, Ph.D.	Registration Number	60890

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Attorney Docket No.: 6683.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Conf. No.: 7802

Application No.: 11/435,977 Group Art Unit: 1654

Filed: May 17, 2006 Examiner: Bradley, Christina

For: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Dear Sir:

In accordance with Applicants' duty of disclosure under 37 C.F.R. § 1.56, and supplemental to the Information Disclosure Statement filed July 28, 2010, Applicants hereby submit the following Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98, and in conformance with MPEP 609 and 37 C.F.R. § 1.98(d).

Applicants hereby make of record the following commonly owned U.S. Applications which may not already be of record in the present application,

- U.S. App. No. 12/785,861, Filed on May 24, 2010, by Flink et al. (Attorney Docket No. 6358.530-US).
- U.S. App. No. 12/752,634, Filed on April 1, 2010, by Schlein et al. (Attorney Docket No. 6711.214-US)

Applicants may also submit herewith Office Actions and, *inter alia*, any documents cited therein, and these documents are listed on the accompanying Form(s) PTO-1449.

The Examiner is encouraged to review any associated Applicant responses in the above mentioned applications, and Applicants assume that due to the ease of review on PAIR by the Examiner, these responses need not be submitted/listed. Since prosecution may be ongoing in the herein mentioned applications, Applicants assume that the Examiner will continue to evaluate the applications as needed.

The Examiner is requested to consider the attached Form PTO-1449, and to return the initialed and signed copy with the next communication from the U.S. Patent and Trademark Office.

Applicants hereby submit two Forms PTO-1449 sheets for consideration by the Examiner in accordance with 37 C.F.R. §§ 1.56, 1.97, and 1.98:

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	2	Atty. Docket No.	6683.204-US

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T
		WO 93/18785	09-30-93	Novo Nordisk A/S		
		WO 01/51071	07-19-01	Novo Nordisk A/S		
		WO 02/47716	06-20-02	Eli Lilly & Co.		
		JP 2003-519195 (corresponds to WO 01/49314)	06-17-03	NPS Allelix Corp.		
		WO 01/49314 (corresponds to JP 2003-519195)	07-12-01	NPS Allelix Corp.		

EXAMINER SIGNATURE		DATE CONSIDERED	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	2	Atty. Docket No.	6683.204-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T
		REMINGTON'S PHARMACEUTICAL SCIENCES, MACK PUBLISHING COMPANY, 16TH EDITION, 1980, CHAPTER 79, PAGE 1406	
		PLUMER'S PRINCIPLES & PRACTICE OF INTRAVENOUS THERAPY, 2006, EDITION 8, PAGES 124-128	
		EUROPEAN PHARMACOPOEIA, 3RD EDITION, 1997, PAGES 17-18	
		UNITED STATES PHARMACOPOEIA, 24TH EDITION, 1999, PAGES 1977-1978	
		FURTHER EXPERIMENTAL DATA	
		FROKJAER ET AL., PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND PROTEINS, 2000, PAGES 145-148 AND 150-151	
		MARTIN ET AL., PHYSICAL PHARMACY: PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES, 1983, PAGE 222	
		REMINGTON'S PHARMACEUTICAL SCIENCES, MACK PUBLISHING COMPANY, 18TH EDITION, 1990, CHAPTER 84, PAGES 1545-1550	
		KNUDSEN ET AL., J. MED. CHEM., VOL. 43, PAGES 1664-1669, 2000	
		STENESH, J., BIOCHEMISTRY, 1998, PAGES 67-69	
		WANG ET AL., J. PARENTERAL SCIENCE AND TECHNOLOGY, VOL. 42, PAGES S4-S26, 1988	
		SIGMA PRODUCTION INFORMATION ON GLY GLY BUFFER, MARCH 2010	
		MARTIN ET AL., PHYSICAL PHARMACY, 1983, PAGE 232	
		DECLARATION OF JOHNNY C. GONZALEZ, NOVEMBER 2010, PAGES 1-7	
		ELI LILLY AND COMPANY PRODUCT INFORMATION ON HUMALOG INSULIN LISPRO INJECTION, 2009, PAGES 1-12	

EXAMINER SIGNATURE		DATE CONSIDERED	

Except for US patent documents a copy of each listed reference is enclosed or submitted herewith.

Copyrighted material submitted with this Information Disclosure Statement may be delivered to the Government under license from the Copyright Clearance Center Inc. or other rights holders – no further reproduction of such works is permitted.

Inclusion of any reference is not intended to constitute an admission that the reference is "prior art" unless it is specifically designated as such.

This Information Disclosure Statement is being filed before the mailing date of a first Office action after the filing of a request for continued examination. Therefore no fee is due. However please charge any fees should they be required to Novo Nordisk Inc. Deposit Account No. 14-1447.

Applicants respectfully request that any references or other information listed above be made of record in this patent application. The Examiner is invited to call the undersigned if there are any questions concerning this submission or application.

Respectfully submitted,

Date: June 10, 2011

/Michael J. Brignati, Reg. No. 60,890/

Michael J. Brignati, Ph.D., Reg. No. 60,890
Novo Nordisk Inc.
Customer Number 23650
(609) 987-5800

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

23650 7590 07/19/2011

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER
BRADLEY, CHRISTINA

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/19/2011

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	10/19/2011

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23650 7590 07/19/2011

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	10/19/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
BRADLEY, CHRISTINA	1654	514-007200

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

23650 7590 07/19/2011

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/19/2011

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 390 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 390 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

Notice of Allowability	Application No.	Applicant(s)
	11/435,977	PEDERSEN ET AL.
	Examiner	Art Unit
	CHRISTINA BRADLEY	1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the RCE filed 06/10/2011*.

2. ☒ The allowed claim(s) is/are *1-9,13-18,28 and 30-44*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)	5. ☐ Notice of Informal Patent Application
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)	6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 06/10/2011	7. ☐ Examiner's Amendment/Comment
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material	8. ☒ Examiner's Statement of Reasons for Allowance
	9. ☐ Other _____.
/Christina Marchetti Bradley/ Primary Examiner, Art Unit 1654	

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 06/10/2011 has been entered.

2. The information disclosure statement (IDS) submitted on 06/10/2011 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

3. Claims 1-9, 13-18, 28 and 30-44 are allowed as they appear in the Examiner's Amendment mailed 12/16/2009 and for the reasons presented in that Office action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 6:00 A.M. to 5:00 P.M.

5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

6. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christina Marchetti Bradley/
Primary Examiner, Art Unit 1654

cmb

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	2	Atty. Docket No.	6683.204-US

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code(if known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T
/C.B./		WO 93/18785	09-30-93	Novo Nordisk A/S		
/C.B./		WO 01/51071	07-19-01	Novo Nordisk A/S		
		WO 02/47716	06-20-02	Eli Lilly & Co.		
/C.B./		JP 2003-519195 (corresponds to WO 01/49314)	06-17-03	NPS Allelix Corp.		
/C.B./		WO 01/49314 (corresponds to JP 2003-519195)	07-12-01	NPS Allelix Corp.		

EXAMINER SIGNATURE		DATE CONSIDERED	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application No.	11/435,977
				Filing Date	May 17, 2006
				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	2	Atty. Docket No.	6683.204-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T
/C.B./		REMINGTON'S PHARMACEUTICAL SCIENCES, MACK PUBLISHING COMPANY, 16TH EDITION, 1980, CHAPTER 79, PAGE 1406	
/C.B./		PLUMER'S PRINCIPLES & PRACTICE OF INTRAVENOUS THERAPY, 2006, EDITION 8, PAGES 124-128	
/C.B./		EUROPEAN PHARMACOPOEIA, 3RD EDITION, 1997, PAGES 17-18	
/C.B./		UNITED STATES PHARMACOPOEIA, 24TH EDITION, 1999, PAGES 1977-1978	
/C.B./		FURTHER EXPERIMENTAL DATA June 22, 2009 /C.B./	
/C.B./		FROKJAER ET AL., PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND PROTEINS, 2000, PAGES 145-148 AND 150-151	
/C.B./		MARTIN ET AL., PHYSICAL PHARMACY: PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES, 1983, PAGE 222-225	
/C.B./		REMINGTON'S PHARMACEUTICAL SCIENCES, MACK PUBLISHING COMPANY, 18TH EDITION, 1990, CHAPTER 84, PAGES 1545-1550	
/C.B./		KNUDSEN ET AL., J. MED. CHEM., VOL. 43, PAGES 1664-1669, 2000	
/C.B./		STENESH, J., BIOCHEMISTRY, 1998, PAGES 67-69	
/C.B./		WANG ET AL., J. PARENTERAL SCIENCE AND TECHNOLOGY, VOL. 42, PAGES S4-S26, 1988	
/C.B./		SIGMA PRODUCTION INFORMATION ON GLY GLY BUFFER, MARCH 2010	
/C.B./		MARTIN ET AL., PHYSICAL PHARMACY, 1983, PAGE 232	
/C.B./		DECLARATION OF JOHNNY C. GONZALEZ, NOVEMBER 2010, PAGES 1-7	
/C.B./		ELI LILLY AND COMPANY PRODUCT INFORMATION ON HUMALOG INSULIN LISPRO INJECTION, 2009, PAGES 1-12	

EXAMINER SIGNATURE	/Christina Bradley/	DATE CONSIDERED	06/16/2011

title for Knudsen et al. "Potent Derivatives of
/C.B./ Glucagon-like Pept~de-1 with Pharmacokinetic Properties Suitable for Once Daily Administration" /CMB/
title for Wang et al. "Parenteral Formulations of Proteins and Peptides: Stability and Stabilizers"

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	11435977	Filing Date	2006-05-17	Docket Number (if applicable)	6683.204-US	Art Unit	1654
First Named Inventor	Tina B. Pedersen			Examiner Name	C. Bradley		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☐ Amendment/Reply

☒ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 14-1447

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Michael J. Brignati, Reg. No. 60,890/	Date (YYYY-MM-DD)	2011-09-13
Name	Michael J. Brignati	Registration Number	60890

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23650 7590 11/01/2011

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER
BRADLEY, CHRISTINA

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/01/2011

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	02/01/2012

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23650 7590 11/01/2011

NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	05/17/2006	Tina Bjeldskov Pedersen	6683.204-US	7802

TITLE OF INVENTION: PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	02/01/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
BRADLEY, CHRISTINA	1654	514-007200

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

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23650 7590 11/01/2011

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
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(application filed on or after May 29, 2000)

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PTOL-85 (Rev. 02/11)

Notice of Allowability	Application No.	Applicant(s)	
	11/435,977	PEDERSEN ET AL.	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

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1. ☒ This communication is responsive to *the RCE filed 09/15/2011*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *1-9,13-18,28 and 30-44*.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

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THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 09/15/2011
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Christina Bradley/
Primary Examiner, Art Unit 1654

ALLOWANCE

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 09/15/2011 has been entered.

The information disclosure statement (IDS) submitted on 09/15/2011 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. It is noted that non-patent literature citation 17 was not considered because a complete legible copy of the reference was not filed. The title page of the book was supplied but not p. 241. It has been placed in the application file, but the information referred to therein has not been considered.

Claims 1-9, 13-18, 28 and 30-44 are allowed as they appear in the Examiner's Amendment mailed 12/16/2009 and for the reasons presented in that Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 6:00 A.M. to 5:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christina Bradley/
Primary Examiner, Art Unit 1654

cmb

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11435977
	Filing Date	2006-05-17
	First Named Inventor	Tina B. Pedersen
	Art Unit	1654
	Examiner Name	C. Bradley
	Attorney Docket Number	6683.204-US

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/C.B./	1	4468346		1984-08-28	Paul et al.	

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/C.B./	1	2000-510813	JP		2000-08-22	GENETICS INSTITUTE INC.	Corresponds to WO9624369	☐
/C.B./	2	2002-504908	JP		2002-02-12	ELI LILLY & CO.	Corresponds to WO9856406	☐
/C.B./	3	2002-524514	JP		2002-08-06	ELI LILLY & CO.	Corresponds to WO0015224 previously submitted	☐

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Receipt date: 09/15/2011	Application Number	11435977 11435977 - GAU: 1654
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2006-05-17
	First Named Inventor	Tina B. Pedersen
(Not for submission under 37 CFR 1.99)	Art Unit	1654
	Examiner Name	C. Bradley
	Attorney Docket Number	6683.204-US

/C.B./	4	0100223	WO		2001-01-04	MINIMED INC.		☐
/C.B./	5	0151071	WO		2001-07-19	NOVO NORDISK		☐
/C.B./	6	2002098445	WO		2002-12-12	CHUGAI PHARMACEUTICAL CO.		☐
/C.B./	7	9318785	WO		1993-09-30	NOVO NORDISK		☐
/C.B./	8	9624369	WO		1996-08-15	GENETICS INSTITUTE	Corresponds to JP 2000-510813	☐
/C.B./	9	9856406	WO		1998-12-17	ELI LILLY & CO.	Corresponds to JP 2002-504908	☐
/C.B./	10	2003519195	JP		2003-06-17	NPS ALLELIX CORP.	Corresponds to WO0149314 previously submitted	☐
/C.B./	11	0247716	WO		2002-06-20	ELI LILLY		☐
/C.B./	12	2306024	CA		1999-04-08	FLEMINGTON PHARMACEUTICAL CORP.		☐
/C.B./	13	2527743	CA		2004-12-09	NOVO NORDISK		☐
/C.B./	14	722492	EP		2005-03-09	UNIVERSITY OF LEEDS INNOVATIONS LTD.		☐

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	Attorney Docket Number	6683.204-US

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/C.B./	1	ELI LILLY & CO., HUMALOG LISPRO INJECTION, USP PRODUCT INFORMATION DATED FEBRUARY 11, 2010	☐
/C.B./	2	European Pharmacopoeia, 3RD EDITION, 2.2.3, 1997, PP. 17-8, Council of Europe-Strasbourg	☐
/C.B./	3	FROKJAER & HOVGAARD, PHARMACEUTICAL FORMULATION DEVELOPMENT OF, 2000, PP. 145- 148 & 150-151	☐
/C.B./	4	FURTHER EXPERIMENTAL DATA DATED JUNE 22, 2009	☐
/C.B./	5	GONZALES, JOHNNY C., DECLARATION OF (INCLUDING CURRICULUM VITA) DATED NOVEMBER 1, 2010 from Patent EP1412384	☐
/C.B./	6	KNUDSEN, L.B. ET AL., POTENT DERIVATIVES OF GLUCOGON-LIKE PEPTIDE-1, JOURNAL OF MEDICINAL CHEMISTRY, 2000, VOL. 43, pp. 1664-9	☐
/C.B./	7	KRISTENSEN, H.G., ALMEN FARMACI, 2000, PP. 273-274, 281	☐
/C.B./	8	MACK PUBLISHING CO., REMINGTON'S PHARMACEUTICAL SCIENCES, 16TH EDITION,1980, PT. 79, pg. 1406	☐
/C.B./	9	MACK PUBLISHING CO., REMINGTON'S PHARMACEUTICAL SCIENCES, 18TH EDITION, 1990, CHAPTER 84, PAGES 1545-50	☐

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	Examiner Name	C. Bradley
	Attorney Docket Number	6683.204-US

/C.B./	10	MARTIN A. ET AL., PHYSICAL PHARMACY; PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES, 1983, 3RD EDITION, PG. 232	☐
/C.B./	11	MARTIN A. ET AL., PHYSICAL PHARMACY; PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES, 1983, 3RD EDITION, PG. 323	☐
/C.B./	12	SIGMA PRODUCT INFORMATION ON GLY-GLY BUFFER DATED MARCH 16, 2010	☐
/C.B./	13	STENESH, J. BIOCHEMISTRY, 1998, PP. 67-9	☐
/C.B./	14	UNITED STATES PHARMACOPOEIA, 24TH EDITION, 1999, PP. 1977-8	☐
/C.B./	15	VILLANUEVA_PENACARRIL, M.L., POTENT GLYCOGNIC EFFECT OF GLP-1(7-36) AMIDE IN RAT SKELETAL MUSCLE, DIABETOLOGIA, 1994, VOL. 37, PP. 1163-6	☐
/C.B./	16	WANG & HANSEN, JOURNAL OF PARENTERAL SCIENCE & TECHNOLOGY, 1988, VOL. 42, pp. 4-26	☐
	17	WANG ET. AL., AGGREGATION OF THERAPEUTIC PROTEINS, 2010, PG. 241 no copy filed	☐
/C.B./	18	WEINSTEIN, SHARON, PLUMER'S PRINCIPLES & PRACTICE OF INTRAVENOUS, 2006, VOL.8 (8), pp. 124-8	☐
/C.B./	19	DUMA ET AL., PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATIONS, VOL. 1, 2ND EDITION, PG. 20	☐

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Receipt date: 09/15/2011	Application Number	11435977 11435977 - GAU: 1654
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2006-05-17
	First Named Inventor	Tina B. Pedersen
	Art Unit	1654
	Examiner Name	C. Bradley
	Attorney Docket Number	6683.204-US

EXAMINER SIGNATURE			
Examiner Signature	/Christina Bradley/	Date Considered	10/21/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

Receipt date: 09/15/2011	Application Number	11435977 11435977 - GAU: 1654
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2006-05-17
	First Named Inventor	Tina B. Pedersen
	Art Unit	1654
	Examiner Name	C. Bradley
	Attorney Docket Number	6683.204-US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Michael J. Brignati, Reg. No. 60,890/	Date (YYYY-MM-DD)	2011-09-13
Name/Print	Michael J. Brignati	Registration Number	60890

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/435,977	02/14/2012	8114833	6683.204-US	7802

23650 7590 01/25/2012

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100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 663 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Tina Bjeldskov Pedersen, Smorum, DENMARK;
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Dorthe Kot Engelund, Holte, DENMARK;