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Address to: Comm P.O. E Alexar This is a request for international applica	Issioner for Patent Sox 1450 Indria, VA 22313-145 filing a X contir tion Number PCTD	s ;0 uuationdiv <2004/000792	isional application under 3 2 , filed on <u>November 1</u>	7 CFR 1.53(b) of pending 8, 2004	prior	3007 U.S. P1 1/435977
entitled PROPYL FOR PRODUC	ENE GLYCOI	L-CONTAIN DR USE IN II	ING PEPTIDE FOI NJECTION DEVIC	RMULATIONS WE	IICH ARE OPTIMAL	
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TOTAL CLAIMS (37 CFR 1.16(i))	44	- 20 =	24	× 50 =	1200.00	
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	DENT CLAIMS (37 C	FR 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	
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8. \overline{X} A declaration under CFR 1.63 is enclosed. (unsigned)	
9. X Priority of foreign application number <u>PA 2003 01719</u> , filed on <u>November 20, 2003</u> , in <u>Denm</u> 119(a)-(d). Priority of US application number60/524,653, filed on November 24, 2003, in <u>the US</u> is clair	<u>ark</u> is claimed under 35 U.S.C. ned 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).
<u>23650</u>	
WARNING: Information on this form may become public. Credit card information be included on this form. Provide credit card information and authorization	ation should not 1 on PTO-2038.
Richard Ev. Bork	May 17, 2006
Signature	Date
Richard W. Bork Typed or printed name	Reg. No. 36,459 Registration Number, if applicable
	(609) 987-5800 Telephone Number
Assignee of the entire interest. See 37 CER 3 71. Statement under 37 CER 3 73(b) is enclosed	(Form PTO/SB/96)
Filed under 37 CFR 1.34 Registration number if acting under 37 CFR 1.34 <u>36,459</u>	
NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representativ Submit multiple forms if more than one signature is required, see below*.	e(s) are required.
\overline{X} *Total of <u>2</u> forms are submitted.	

[Page 2 of 2]

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

PROPYLENE PEPTIDE Title: **GLYCOL-CONTAINING** 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) Rachida Haji (Signature of person mailing paper(s) or fee)

Mailing Address: Novo Nordisk Inc. Customer Number 23650

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



TENT TRADEMARK OFFIC

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

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CROSS REFERENCE TO RELATED APPLICATIONS

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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.

10 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

15 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.

- 20 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
- 25 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.

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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 fornulations 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;

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- 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.
- 25 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
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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.

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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 formula-

15 tion 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

20 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.

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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 Arg³⁴, Lys²⁶(N^ε-(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.

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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} , $Lys^{26}(N^{\epsilon}-(\gamma-Glu(N^{\alpha}-hexadecanoyl)))-GLP-1(7-37)$ medium containing myo-inositol.

10 Figure 6 shows deposits on filling equipment after 24 hours simulated filling with a mannitolcontaining placebo formulation.

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

DESCRIPTION OF THE INVENTION

- 20 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 simu-
- 30 lated 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, angio-

35 tensin, 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

5 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 an-

- 10 other 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,
- 15 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 20 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

- 25 agonist" is any peptide that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC₅₀) 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
- 30 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

35 (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).

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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

15 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(CH₂)_mCO-, wherein m is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is HOOC(CH₂)₁₄CO-, HOOC(CH₂)₁₆CO-, HOOC(CH₂)₁₈CO-, HOOC(CH₂)₂₀CO- or HOOC(CH₂)₂₂CO-.

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,

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(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.

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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 epsilonamino 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

20 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

25 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 gammaaminobutanoyl, 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

- 30 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
- 35 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^s-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

5 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 $CH_3(CH_2)_pNH-CO(CH_2)_qCO$ -, 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 $CH_3(CH_2)_rCO$ -NHCH(COOH)(CH₂)₂CO-, 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 $CH_3(CH_2)_sCO-NHCH((CH_2)_2COOH)CO-$, 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 $COOH(CH_2)_tCO$ - 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 -NHCH(COOH)(CH₂)₄NH-CO(CH₂)_uCH₃, 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 $CH_3(CH_2)_vCO-NH-(CH_2)_z-CO$, 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 -NHCH(COOH)(CH₂)₄NH-COCH((CH₂)₂COOH)NH-CO(CH₂)_wCH₃, 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 -NHCH(COOH)(CH₂)₄NH-CO(CH₂)₂CH(COOH)NHCO(CH₂)_xCH₃, 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} , $\operatorname{Lys}^{26}(N^{\epsilon}-(\gamma-\operatorname{Glu}(N^{\alpha}-\operatorname{hexade-} 30 \operatorname{canoyl})))$ -GLP-1(7-37).

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide, Val⁸-GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Clu²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-37), Val⁸Clu²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-37), Val⁸Arg²²-

35 GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-37), Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-37), analogues thereof and derivatives of any of these.

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Val⁸Glu²²His³⁷-GLP-1(7-37), Val⁸Glu²²Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵ 37), Val⁸Trp¹⁶Glu²²Ile³³-GLP-1(7-37), Val⁸Glu²²Val²⁵Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵ GLP-1(7-37), analogues thereof and derivatives of any of these.

- 1(7-36)-amide; Met⁸His²²His³⁷-GLP-1(7-36)-amide; and derivatives thereof.
 In yet another embodiment the GLP-1 agonist is selected from the group consisting of Val⁸Trp¹⁹Glu²²-GLP-1(7-37), Val⁸Glu²²Val²⁵-GLP-1(7-37), Val⁸Trp¹⁶Glu²²-GLP-1(7-37), Val⁸Leu¹⁶Glu²²-GLP-1(7-37), Val⁸Trp¹⁶Glu²²-GLP-1(7-37), Val⁸Clu²²He³³-GLP-1(7-37), Val⁸Clu²²Val²⁵He³³-GLP-1(7-37), Val⁸Clu²²
- 25 1(7-36)-amide; Gly⁸His³⁷-GLP-1(7-36)-amide; Val⁸His³⁷-GLP-1(7-36)-amide; Met⁸His³⁷-GLP-1(7-36)-amide;
 1(7-36)-amide; Gly⁸Asp²² His³⁷-GLP-1(7-36)-amide; Val⁸Asp²²His³⁷-GLP-1(7-36)-amide;
 Met⁸Asp²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Met⁸Glu²²His³⁷-GLP-1(7-36)-amide;
 1(7-36)-amide; Gly⁸Lys²² His³⁷-GLP-1(7-36)-amide; Val⁸Lys²²His³⁷-GLP-1(7-36)-amide;
 Met⁸Lys²²His³⁷-GLP-1(7-36)-amide; Gly⁸Arg²²His³⁷-GLP-1(7-36)-amide; Val⁸His²²His³⁷-GLP-1(7-36)-amide;
- GLP-1(7-36)-amide; Met⁸Glu²²-GLP-1(7-36)-amide; Gly⁸Lys²²-GLP-1(7-36)-amide; Val⁸Lys²²-GLP-1(7-36)-amide; Met⁸Lys²²-GLP-1(7-36)-amide; Gly⁸Arg²²-GLP-1(7-36)-amide; Val⁸Arg²²-GLP-1(7-36)-amide; Met⁸Arg²²-GLP-1(7-36)-amide; Gly⁸His²²-GLP-1(7-36)-amide; Val⁸His²²-GLP-1(7-36)-amide; Met⁸His²²-GLP-1(7-36)-amide; His³⁷-GLP-1(7-36)-amide; Val⁸Arg²²His³⁷-GLP-1(7-36)-amide; Met⁸Arg²²His³⁷-GLP-1(7-36)-amide; Met⁸Arg²²-GLP-1(7-36)-amide; Met⁸His²²-GLP-1(7-36)-amide; Met⁸Arg²²-GLP-1(7-36)-amide; Met⁸-Arg²²-GLP-1(7-36)-amide; Met⁸-Arg²
- Arg³⁴-GLP-1(7-36)-amide; Lys³⁶-GLP-1(7-36)-amide; Arg^{26,34}Lys³⁶-GLP-1(7-36)-amide; Arg^{26,34}-GLP-1(7-36)-amide; Arg^{26,34}Lys³⁶-GLP-1(7-36)-amide; Arg³⁴Lys³⁶-GLP-1(7-36)-amide; Gly⁸-GLP-1(7-36)-amide; Val⁸-GLP-1(7-36)-amide; Met⁸-GLP-1(7-36)-amide; Gly⁸-GLP-1(7-36)-amide; Gly⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; Val⁸-GLP-1(7-36)-amide; Val⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; Val⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; Val⁸-GLP-1(7-36)-amide; ClP⁸-GLP-1(7-36)-amide; ClP⁹-GLP-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁸-1(7-36)-amide; ClP⁸-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁹-1(7-36)-amide; ClP⁹-1(7-36)-1(7-36)-amide; ClP⁹-1(7-36)-1(7-36)-1(7-36)-1(7-
- 37);Gly⁸Arg²²His³⁷-GLP-1(7-37); Val⁸Arg²²His³⁷-GLP-1(7-37); Met⁸Arg²²His³⁷-GLP-1(7-37);
 Gly⁸His²²His³⁷-GLP-1(7-37); Val⁸His²²His³⁷-GLP-1(7-37); Met⁸His²²His³⁷-GLP-1(7-37);
 Gly⁸His³⁷-GLP-1(7-37); Val⁸His³⁷-GLP-1(7-37); Met⁸His³⁷-GLP-1(7-37); Gly⁸Asp²² His³⁷-GLP-1(7-37);
 Val⁸Asp²²His³⁷-GLP-1(7-37); Met⁸Asp²²His³⁷-GLP-1(7-37); Arg²⁶-GLP-1(7-36)-amide;
 Arr³⁴ Ol D 4/7 20) arridation Arr^{26,34}
- Met⁸-GLP-1(7-37); Gly⁸Asp²²-GLP-1(7-37); Val⁸Asp²²-GLP-1(7-37); Met⁸Asp²²-GLP-1(7-37); Gly⁸Glu²²-GLP-1(7-37); Val⁸Glu²²-GLP-1(7-37); Met⁸Glu²²-GLP-1(7-37); Gly⁸Lys²²-GLP-1(7-37); Val⁸Lys²²-GLP-1(7-37); Gly⁸Arg²²-GLP-1(7-37); Val⁸Lys²²-GLP-1(7-37); Gly⁸Glu²²His³⁷-GLP-1(7-37); Val⁸Glu²²His³⁷-GLP-1(7-37); Met⁸Glu²²His³⁷-GLP-1(7-37); Met⁸Glu
- In yet another embodiment the GLP-1 agonist is selected from the group consisting of Arg²⁶-GLP-1(7-37); Arg³⁴-GLP-1(7-37); Lys³⁶-GLP-1(7-37); Arg^{26,34}Lys³⁶-GLP-1(7-37); Arg^{26,34}-GLP-1(7-37); Arg^{26,34}Lys⁴⁰-GLP-1(7-37); Arg²⁶Lys³⁶-GLP-1(7-37); Arg³⁴Lys³⁶-GLP-1(7-37); Val⁸Arg²²-GLP-1(7-37); Met⁸Arg²²-GLP-1(7-37); Gly⁸His²²-GLP-1(7-37); Val⁸His²²-GLP-1(7-37); Met⁸His²²-GLP-1(7-37); His³⁷-GLP-1(7-37); Gly⁸-GLP-1(7-37); Val⁸-GLP-1(7-37);

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

5 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

10 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-15 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: <u>Nature</u>, (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^{LB29}-octanoyl insulin, 30/70 mixtures of prompt insulin zinc
- 30 (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.

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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

20 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

30 which comprises at least 6 carbon atoms; and 2-4 Zn²⁺ 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 Zn²⁺ 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

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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

10 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 Zn²⁺ 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 MethGH, 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.

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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.

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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

- 25 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.
- 30 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
- 35 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

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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

10 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

15 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*

20 *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

- 25 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.
- 30 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 mo-
- 35 lecular 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

5 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-

10 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.

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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.

- 20 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,
- 25 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
- 30 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-1propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (e.g. cetyltrimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants,

- 5 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^αacylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of
- 10 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.
- 15 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*

20 *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 inventioncontain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

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

In another embodiment, the method for preparing such a peptide formulation com-

prises:

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

tion 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

30 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

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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 un-

- 5 derstood 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
- 10 (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.

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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 formula-

10 tion 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.

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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.

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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.

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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

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

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filtered through a 0.22 μ m filter. The isotonic agents tested in each formulation and their concntrations are shown in Table 1.

Formulation	Tonicity modifier
no.	
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)

 Table 1
 Composition of the tested formulations

5 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

10 (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.

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		

Table 2. The measured osmolarity of the formulations

Drop test

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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} , $Lys^{26}(N^{\epsilon}-(\gamma-Glu(N^{\alpha}-hexadecanoyl)))-GLP-1(7-37)$.

10 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

15 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.

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						<u></u>		
(90)	10	0	0	0	0	2	0	43
Glycerol					. <u> </u>			
(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				-	12 (5 at			
(90)	25	1	0	0	needle)	0	0	0
arginin					3 (2 at			
(90)	26	2	0	0	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					16 (7 at			(1 at
(90)	32	11	5	0	needle)	1	0	needle)
glycine					1 (2 at			31 (2 at
(90)	41	9	2	0	needle)	0	0	needle)
maltose					16 (6 at			1 (5 at
(90)	35	8	7	4	needle)	00	0	needle)
laktose								31 (2 at
(90)	44	10	8	0	5	0	0	needle)

Table 3 Clogging test in NovoPen 1.5 using 30G NovoFine

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

5 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

5 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

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In the simulated filling experiment xylitol, glycerol, glucose, maltose, PEG 400, propylene glycol,

- 10 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 re-
- 15 placements 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 Arg³⁴, Lys²⁶(N^ε-(γ-Glu(N^α-hexadecanoyl)))-GLP-1(7-37)-containing formulations;
 - 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

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EXAMPLE 2

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

Preparation of Formulations

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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 μ m filter. The compositions of the formulations were as follows:

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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

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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 formula-

20 after 24 hours, a lot tion (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 Arg³⁴, Lys²⁶(N[€]-(γ-Glu(N^α-hexadecanoyl)))-GLP-1(7-37) Containing Formulations

Preparation of Formulations

5 Preservative, isotonic agent (mannitol or propylene glycol) and buffer were dissolved in water and pH was adjusted to the desired pH. Arg³⁴, Lys²⁶(N^ε-(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:

Arg³⁴, Lys²⁶(N^ε-(γ-Glu(N^α-hexadecanoyl)))-GLP-1(7-37) (6.25 mg/ml), 10 Disodium hydrogen phosphate, dihydrate (1.42 mg/ml), Phenol (5.5 ma/ml), mannitol or propylene glycol (35.9 or 14.0 mg/ml), Water for Injection (up to 1.0 ml), pH: 8.15

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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 20 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 25 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

30 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

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Example 4

Influence of Peptide Concentration On Clogging of Needles

Arg³⁴, Lys²⁶(N^{ϵ}-(γ -Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) formulations were prepared as de-

10 scribed in Example 3 using peptide concentrations ranging from 0-5 mg/ml of Arg³⁴, Lys²⁶(N^ε-(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

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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.

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Example 5

Clogging of needles in Lys &29 (N ϵ -tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations Containing Mannitol

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Preparation Of Formulations

The Lys &29 (N ϵ -tetradecanoyl) des(B30) human insulin-containing formulation was prepared as follows:

a) Prepared a first solution by dissolving buffer, sodium chloride, preservatives (phenol and

35 m-cresol) and mannitol in water

b) Prepared a second solution of Lys &29 (N ϵ -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

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The composition of Lys β 29 (N ϵ -tetradecanoyl) des(B30) human insulin-containing formulation prepared in the above manner was as follows:

Lys ß29 (N ϵ -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

10 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
- 15 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) Adjusted the pH of the solution to the desired pH and crystallized at room temperature
- 20 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 &29 (N ϵ -tetradecanoyl) des(B30) human insulin on day 2

5 (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 Arg³⁴, Lys²⁶(N^ε-(γ-Glu(N^α-hexadecanoyl)))-GLP-1(7-37), Lys ß29 (N*ε*-tetradecanoyl) des(B30) human insulin and NovoMix 30.

Example 6

Testing of Lys β 29 (N ϵ -tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations containing propylene glycol

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The preparation and composition of the Lys ß29 (N ϵ -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.

- 20 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 Arg³⁴, Lys²⁶(N^ε-(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 (Nεtetradecanoyl) des(B30) human insulin and NovoMix 30-containing formulations will be simi-
- 25 Iar to that observed with Arg³⁴, Lys²⁶(N^ε-(γ -Glu(N^α-hexadecanoyl)))-GLP-1(7-37)-containing formulations.

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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

5 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.

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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 isfrom 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.

20 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.

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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.

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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.

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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.

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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.

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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.

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17. The formulation according to claim 16, wherein said GLP-1 agonist is Arg^{34} , $\text{Lys}^{26}(\text{N-}\epsilon-(\gamma-Glu(\text{N-}\alpha-hexadecanoyl)))-GLP-1(7-37).$

The formulation according to claim 12, wherein said GLP-1 agonist is selected from the
 group consisting of Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide,
 Val⁸-GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Lys²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide,
 Val⁸His²²-GLP-1(7-37), Arg34GLP-1(7-37); Arg26,34,Lys36GLP-1(7-36); Arg26GLP-1(7-37);

25 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 fore-going.

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.

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21. The formulation according to claim 20, wherein the insulin derivative is Lys β 29 (N ϵ -tetradecanoyl) des(B30) human insulin.

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

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

10 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.

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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.

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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

25 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.
- 35 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.

5 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.

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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.

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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.

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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.

30 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 glycolcontaining formulation that must be discarded due to deposits relative to number of vials
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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

15 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.

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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

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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.

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FIGURE 1

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FIGURE 3



Myo-inositol









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FIGURE 4



Glycine

Lactose

Mannitol

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FIGURE 5



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FIGURE 6



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FIGURE 7



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COMBINED DECLARATIO	ON FOR PATENT APPLICATIOn Provide Applications)	ON AND POWER OF ATTORN	EY Attorney's Docket Number: 6683.204-US
As a below named inv	entor, I hereby declare that:		
My residence, post of	fice address and citizenship are as	stated below next to my name.	
I believe I am the orig joint inventor (if plur patent is sought on the	inal, first and sole inventor (if on al names are listed below) of th invention entitled:	ly one name is listed below) or an e subject matter which is claimed	original, first and and for which a
PROPYLENE GLY FOR PRODUCTIO	COL-CONTAINING PEPTID	E FORMULATIONS WHICH A ON DEVICES	RE OPTIMAL
The specification of w [x] is attached he [] was filed as U	hich (check only one item below) ereto Jnited States application	:	
Application No. <u>T</u>	o Be Assigned		
on <u>May 17, 2006</u> and was amended on			
[] was filed as PCT in Number	nternational application		
onand was amended und on	er PCT Article 19		
I hereby state that I including the claims, a	have reviewed and understand s amended by an amendment refe	the contents of the above-identif rred to above.	ied specification,
I acknowledge the du accordance with Title	ity to disclose information which 37, Code of Federal Regulations,	n is material to patentability of th §1.56.	nis application in
I hereby claim priorit application(s) for pate inventor's certificate of the United States of A patent or inventor's ce than the United States the application(s) of w	y benefits under Title 35, United nt or inventor's certificate or of or of any PCT international applic America listed below and have a rtificate or any PCT international of America filed by me on the sa hich priority is claimed:	d States Code, §119 of any provi any PCT international application ations(s) designating at least one c lso identified below any foreign application(s) designating at least me subject matter having a filing d	isional or foreign (s(s) for patent or country other than application(s) for one country other late before that of
PRIOR U.S. PROVISIONAL/F	OREIGN/PCT APPLICATION(S	S) AND ANY PRIORITY CLAIM	S UNDER 35 U.S.C. 119:
COUNTRY (if PCT, indicated "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
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

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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)				6683.204-	Attorney's Docket Number: 6683.204-US		
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	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	<u></u>	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	Family Name		First Given Name	Second Given Name
	Residence & Citizenship	City	<u></u>	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
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	l hereby decl further that th section 1001	are that all statements made herein of asse statements were made with the kr of Title 18 of the United States Code,	f my own knowledg nowledge that willfu and that such willful	e are true and that all statements made on informati I false statements and the like so made are punishab false statements may jeopardize the validity of the a	on and belief are believed to be true; and le by fine or imprisonment, or both, under application or any patent issuing thereon.
Signa	ture of Inventor 1		Signature of Inven	tor 2	Signature of Inventor 3
Date			Date		Date
Signa	ture of Inventor 4		Signature of Inven	tor 5	Signature of Inventor 6
Date		······			
Signat	ture of Inventor 7		Signature of Inven	tor ð	Signature of Inventor 9
Date			Date		Date

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Attorney Docket No.: 6683.204-US

PATENT

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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

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

4

<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 <211> 44 <212> PRT <213> Synthetic construct <220> <221> MOD_RES <222> (44)..(44) <223> Lysine at position 44 is amidated <400> 1 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 5 10 15 1 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 35 40

PTO/S8/06 (12-04)



If you need assistance in completing the form,

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 52 of 283

PATENT APPLICATION SERIAL NO.

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

9005/22/2006	MAHMEDI	00000004	141447	11435977
	100000	*******		

01	FC:1011	300.00	DA
20	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 Priviling Office: 2002 - 489-267/8903

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 53 of 283

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		
City of Residence::	Ballerup		
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	DK-2750		
address::			
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	DK-2800		
address::			
Applicant Authority Type::	Inventor		

Attorney Docket No.: 6683.204-US

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Page 2 of 4

May. 17, 06

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 55 of 283

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	DK-2840
address::	

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	

May. 17, 06

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

May. 17, 06



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torney 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:

WO 2005/046716
 WO 93/23010
 WO 95/13825
 WO 99/16417
 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.

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Date: July 10, 2006

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,

Richard W. Bork, Reg. No. 36,459

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

						Sheet 1 of		
FORM PTO-1449 (Rev. 2-32)	U.S. DEPART PATENT AND	MENT OF COMMERCE	Atty. Docket No. 6683.204	-US	Serial No. 11/4	Serial No. 11/435,977		
AF & Was	INFORMATION DISCLOSURI STATEMENT BY APPLICANT	E r	Applicant Pedersen et a	I				
7 2006	Use several sheets if necessary))	Filing Date May 17, 2000	6	Group 1646			
JUL	/	U.S. PAT	ENT DOCUMENTS					
BAMINER BURN	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE		
	2002/0151467	12/21/00	Leung, F.K.					
	5206219	11/25/91	Applied Analytical Industries, INC					

FOREIGN PATENT DOCUMENTS								
	DOCUMENT					TRANS	LATION	
	NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	YES	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	1 <i>, </i>	5 e	t al	_	Aaps	Pharms	scitech	1 –	2003	_ `	Vol.	4 -	- Part	3-Pgs	3.334-	342
			_																
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EXAMINER		-	-							DATE COM	SIDE	RED							

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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59-1-06

17.00

0 8 2006 [®] Attorney Docket No.: 6683.204-US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al.

Serial No.: 11/435,977

Group Art Unit: 1646

Confirmation No.: 7802

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 Haii (name of person mailing paper) of (signature) person



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al.Confirmation No.: 7802Serial No.: 11/435,977Group Art Unit: 1646Filed: May 17, 2006Examiner: 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

Richard W. Bork, Reg. No. 36,4 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

	/	UIPE	Page 1 of 2	
UNITED STATE	S PATENT AND TRADEN	د SEP 0 8 2006 ⁵⁰ RK OFFICER	09-11-04	100
		UNITED S United St Address CO Address CO	STATES DEPARTMENT OF COMMERCE ates Patent and Trademark Office MISSIONER FOR PATENTS Box 1430 motia, Virginia 22313-1450 surpto.gov	
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	
23650 NOVO NORDISK, INC. PATENT DEPARTMENT			CONFIRMATION NO. 7802 FORMALITIES LETTER	

Date Mailed: 06/12/2006

3

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:

100 COLLEGE ROAD WEST PRINCETON, NJ 08540

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.

To Download Patentin Software, visit http://www.uspto.gov/web/patents/software.htm For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (571) 272-0951
- For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.
- Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

• To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of \$130 for a non-small entity, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is \$130 for a Large Entity

• \$130 Surcharge.

Replies should be mailed to:	Mail Stop Missing Parts
	Commissioner for Patents
	P.O. Box 1450
	Alexandria VA 22313-1450

A copy of this notice <u>MUST</u> be returned with the reply.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382 PART 2 - COPY TO BE RETURNED WITH RESPONSE



FILED UNDER 37 CFR 1.53(b)

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.

L.

 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.

To Download Patentin Software, visit http://www.uspto.gov/web/patents/software.htm For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (571) 272-0951
- For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.
- Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

• To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of \$130 for a non-small entity, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is \$130 for a Large Entity

• \$130 Surcharge.

Replies should be mailed to: Mail Stop Missing Parts Commissioner for Patents P.O. Box 1450 Alexandria VA 22313-1450

A copy of this notice <u>MUST</u> be returned with the reply.

Billeblemoi 2

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382 PART 1 - ATTORNEY/APPLICANT COPY

COMBINED DECLARATIO (Includes Reference to PCT Int	N FOR PATENT APPLICATIO ernational Applications)	ON AND POWER OF ATTORN	EY Attorney's Booket Number: 66833044US
As a below named inv	entor, I hereby declare that:		(SEP 0 8 2006)
My residence, post off	ice address and citizenship are as	stated below next to my name.	ATT A STATE
I believe I am the orig joint inventor (if plur patent is sought on the	inal, first and sole inventor (if on al names are listed below) of the invention entitled:	ly one name is listed below) or an subject matter which is claimed	original, first and and for which a
PROPYLENE GLY FOR PRODUCTIO	COL-CONTAINING PEPTIDE	C FORMULATIONS WHICH AN ON DEVICES	RE OPTIMAL
The specification of w [x] is attached he [] was filed as U	hich (check only one item below): reto Jnited States application		
Application No. 1	1/435,977		
on May 17, 2006			
and was amended			
[] was filed as PCT in Number	nternational application		
and was amended und	er PCT Article 19		
I hereby state that I including the claims, a	have reviewed and understand s amended by an amendment refer	the contents of the above-identifing to above.	ed specification,
I acknowledge the du accordance with Title	ty to disclose information which 37, Code of Federal Regulations,	i is material to patentability of th §1.56.	is application in
I hereby claim priorit application(s) for pate inventor's certificate of the United States of J patent or inventor's ce than the United States the application(s) of w	y benefits under Title 35, United ent or inventor's certificate or of or of any PCT international applic America listed below and have a prtificate or any PCT international of America filed by me on the sam thich priority is claimed:	d States Code, §119 of any provi any PCT international application ations(s) designating at least one c lso identified below any foreign a application(s) designating at least on me subject matter having a filing d	sional or foreign s(s) for patent or ountry other than application(s) for one country other ate before that of
PRIOR U.S. PROVISIONAL/F	FOREIGN/PCT APPLICATION(S	S) AND ANY PRIORITY CLAIMS	S UNDER 35 U.S.C. 119:
COUNTRY (if PCT_indicated "PCT")		DATE OF FILING	PRIORITY CLAIMED
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

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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		
I here Amer provio Regul	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. APPLICATIO	NS OR PCT INTER	NATIONAL APPLICATIONS DESIGNATIN UNDER 35 U.S.C. 120:	NG THE U.S. FOR BEN	JEFIT			
			U.S. AP	PLICATIONS		ST	TUS (Check one	:)		
	U.S. APPLIC	ATION NUMB	ER		U.S. FILING DATE	Patented	Pending	Abandoned		
					<u>_</u>					
		РСТ	APPLICATIONS	DESIGNATING TH	1E U.S.					
	APPLICATION 1	NO.	FILI	NG DATE	US SERIAL NUMBERS ASSIGNED (if any)					
PCI	ſ/DK2004/00	0792	18 Nove	ember 04			x			
						-				
POWI and/or Bork	ER OF ATTORNEY agent(s), to prosecu	: As a named te this applicati	inventor, I hereby ion and transact al	appoint the attorney business in the Pat	(s) and/or agent(s) associated with Custome ent and Trademark Office connected therew Wilk Oraccon Reg. No. 45 320: Let	er Number 23650, inclu ith. Reza Green, Reg	ding the following at g.No. 38,475; Rich	tomey(s) hard W.		
DOIN	, 106, 110, 50, 159,			,027, 1030112110	K. Wilk-Stessall, Keg. 110. 45,220, Ed.	1 3. Shini, Keg. 10.	-5.157			
Senc	I Correspondence to	 Reza Green, Novo Nordisl 100 College I Princeton, NJ 	Esq. k Pharmaceuticals, Road West 0840	Inc.		Direct 1 Reza (609	irect Telephone Calls To: Reza Green (609) 987-5800			
1	Full Name of Inventor	Family Na	me		First Given Name	Second	Second Given Name			
	Residence &	Peders	sen		Tina State or Foreign Country	Bje	Bjeldskov Country of Citizenship			
	Citizenship	Smøru Bost Office	m		Denmark	Den	Denmark			
	Address	Kongel	haven 9		Smarum	DK-	rk			
2	Full Name of	Family Nat	me		First Given Name	Second	Second Given Name			
	Inventor	Bonde			Claude					
	Residence & Citizenship	City			State or Foreign Country	Country	of Citizenship			
	Post Office	Post Office	Address		Denmark City	Fran State &	ICE Zip Code/Country			
	Address	Borgev	ej 41 B		Lyngby	DK-2	2800/Denmar	·k		
3	Full Name of	Family Nai	me		First Given Name	Second	Given Name	-		
	Engelund			Dorthe States Grant and States an	Kot	- Chieren bie				
	Kesidence & Citizenship				State or Poreign Country	Country	or Citizenship			
	Holte Post Office Post Office Address			City	State &	IIAFK Zip Code/Country				
	Address	Gasseh	aven 39		Holte	DK-2	2840/Denmar	·k		
4	Full Name of Inventor	Family Na	me		First Given Name	Second	Given Name			
	Residence & Citizenship	City			State or Foreign Country	Country	Country of Citizenship			
	Post Office Post Office Address Address				City	State &	Zip Code/Country			

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2 of 3

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 69 of 283

COl (Inc	MBINED DEC ludes Reference	LARATION FOR PATENT to PCT International Applica	CAPPLICATE ations)	ON AND POWER OF ATTORNEY	Attor: 6683	ney's Docket Number: 3.204-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	<u>. </u>	City		State & Zip Code/Country	
7	Full Name of Inventor	Family Name		First Given Name		Second Given Name	
	Residence & Citizenship	City	<u></u> "	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	
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<120>	Propylene glycol-containing peptide formulations
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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.



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Patent- og Varemærkestyrelsen Økonomi- og Erhvervsministeriet

28 April 2006

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Pia Høybye-Olsen

ന്നാ PATENT- OG VAREMÆRKESTYRELSEN

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 72 of 283
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 formu-5 lations 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 10

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 equip-

- 15 ment 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 20
 - 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. 11.1.185

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SUMMARY OF THE INVENTION

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[•] 30

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-

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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.

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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;

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- 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.

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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

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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 be-

15 tween 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.

20 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} , $\operatorname{Lys}^{26}(N^{\epsilon}-(\gamma-\operatorname{Glu}(N^{\alpha}-\operatorname{hexadecanoyl})))-GLP-1(7-$ 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.

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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.

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

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Figure 6 shows deposits on filling equipment after 24 hours simulated filling with a mannitolcontaining 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 Arg³⁴, Lys²⁶(N^ε-(γ-Glu(N^α-hexadecanoyl)))-GLP-1(7-37) formulations.

DESCRIPTION OF THE INVENTION

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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 produc- ** tion 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 de-

vices 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-

30 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 hormonereleasing factor, pituitary adenylate cyclase activating peptide, secretin, enterogastrin, somatostatin, somatomedin, parathyroid hormone, thrombopoietin, erythropoietin, hypothalamic re-

leasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, oxytocin, opiods, DPP IV, interleukins, immunoglobulins, complement inhibitors, serine protease

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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 (EC₅₀) 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 <u>in vivo</u> or <u>in vitro</u> assays known to those of ordinary skill in the art.

25 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
- 35 (Eli Lilly & Co.), EP 0708179-A2 (Eli Lilly & Co.), EP 0699686-A2 (Eli Lilly & Co.), WO
 01/98331 (Eli Lilly & Co).

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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 lipo-philic 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

10 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 20 CH₃(CH₂)_nCO-, wherein n is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is CH₃(CH₂)₁₂CO-, CH₃(CH₂)₁₄CO-, CH₃(CH₂)₁₆CO-, CH₃(CH₂)₁₈CO-, CH₃(CH₂)₂₀CO- and CH₃(CH₂)₂₂CO-. 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(CH₂)_mCO-, wherein m is an integer from 4 to 38, preferably an integer from
 12 to 38, and most preferably is HOOC(CH₂)₁₄CO-, HOOC(CH₂)₁₆CO-, HOOC(CH₂)₁₈CO-,
 HOOC(CH₂)₂₀CO- or HOOC(CH₂)₂₂CO-.

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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,

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

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

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(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 5 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 epsilonamino 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, and an amino group of the amino acid residue or dipeptide spacer.

Preferred spacers are lysyl, glutamyl, asparagyl, glycyl, beta-alanyl and gammaaminobutanoyl, 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^c-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 $CH_3(CH_2)_pNH-CO(CH_2)_qCO$ -, 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 $CH_3(CH_2)$, CO-NHCH(COOH)(CH₂)₂CO-, 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 $CH_3(CH_2)_sCO-NHCH((CH_2)_2COOH)CO-$, wherein s is an integer from 4 to 24, \sim preferably from 10 to 24.

In a further embodiment, the lipophilic substituent is a group of the formula $COOH(CH_2)_1CO$ - 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 -NHCH(COOH)(CH₂)₄NH-CO(CH₂)_uCH₃, 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 $CH_3(CH_2)_vCO-NH-(CH_2)_z$ -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 -NHCH(COOH)(CH₂)₄NH-COCH((CH₂)₂COOH)NH-CO(CH₂)_wCH₃, 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 -NHCH(COOH)(CH₂)₄NH-CO(CH₂)₂CH(COOH)NHCO(CH₂)_xCH₃, wherein x is zero or an integer from 1 to 22, preferably 10 to 16.

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

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide, GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-36)-amide,

30 Val⁸Glu²²-GLP-1(7-37), Val⁸Lys²²-GLP-1(7-36)-amide, Val⁸Lys²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-37), Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-37), val⁸His²²-GLP-1(7-37

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Arg²⁶-GLP-1(7-37); Arg³⁴-GLP-1(7-37); Lys³⁶-GLP-1(7-37); Arg^{26,34}Lys³⁸-GLP-1(7-37);

Arg^{26.34}-GLP-1(7-37); Arg^{28,34}Lys⁴⁰-GLP-1(7-37); Arg²⁶Lys³⁶-GLP-1(7-37); Arg³⁴Lys³⁸-GLP-1(7-37);
 Yal⁸Arg²²-GLP-1(7-37); Met⁸Arg²²-GLP-1(7-37); Glv⁸His²²-GLP-1(7-37); Val⁸His²²-GLP-1(7-37);

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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

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- 1(7-37); Met⁸His²²-GLP-1(7-37);His³⁷-GLP-1(7-37); Gly⁸-GLP-1(7-37); Val⁸-GLP-1(7-37); Met⁸-GLP-1(7-37); Gly⁸Asp²²-GLP-1(7-37); Val⁸Asp²²-GLP-1(7-37); Met⁸Asp²²-GLP-1(7-37); Gly⁸Glu²²-GLP-1(7-37); Val⁸Glu²²-GLP-1(7-37); Met⁸Glu²²-GLP-1(7-37); Gly⁸Lys²²-GLP-1(7-37); Val⁸Lys²²-GLP-1(7-37); Met⁸Lys²²-GLP-1(7-37); Met⁸Lys²²-GLP-1(7-37); Val⁸Lys²²-GLP-1(7-37); Met⁸Lys²²-GLP-1(7-37); Met⁸Lys²²-GLP-1(7-37); Met⁸Lys²²-GLP-1(7-37); Met⁸Glu²²His³⁷-GLP-1(7-37); Gly⁸Glu²²His³⁷-GLP-1(7-37); Met⁸Glu²²His³⁷-GLP-1(7-37); Met⁸Glu²²His³⁷-GLP-1(7-37); Met⁸Clu²²-GLP-1(7-37); Met
- Met⁸Glu²²His³⁷-GLP-1(7-37);Gly⁸Lys²² His³⁷-GLP-1(7-37); Met⁸Lys²²His³⁷-GLP-1(7-37);Gly⁸Arg²²His³⁷-GLP-1(7-37); Val⁸Arg²²His³⁷-GLP-1(7-37); Met⁸Arg²²His³⁷-GLP-1(7-37); Gly⁸His²²His³⁷-GLP-1(7-37); Val⁸His²²His³⁷-GLP-1(7-37); Met⁸His²²His³⁷-GLP-1(7-37); Gly⁸His³⁷-GLP-1(7-37); Val⁸His³⁷-GLP-1(7-37); Met⁸His³⁷-GLP-1(7-37);Gly⁸Asp²² His³⁷-GLP-
- 10 1(7-37); Val⁸Asp²²His³⁷-GLP-1(7-37); Met⁸Asp²²His³⁷-GLP-1(7-37); Arg²⁸-GLP-1(7-36)-amide; Arg³⁴-GLP-1(7-36)-amide; Lys³⁶-GLP-1(7-36)-amide; Arg^{28,34}Lys³⁶-GLP-1(7-36)-amide; Arg^{28,34}-GLP-1(7-36)-amide; Arg^{26,34}Lys⁴⁰-GLP-1(7-36)-amide; Arg²⁶Lys³⁶-GLP-1(7-36)-amide; Arg³⁴Lys³⁶-GLP-1(7-36)-amide; Gly⁸-GLP-1(7-36)-amide; Val⁸-GLP-1(7-36)-amide; Met⁸-GLP-1(7-36)-amide; Gly⁸Asp²²-GLP-1(7-36)-amide; Gly⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Asp²²-
- 15 GLP-1(7-36)-amide; Met⁸Asp²²-GLP-1(7-36)-amide;Gly⁸Glu²²-GLP-1(7-36)-amide; Val⁸Glu²²-GLP-1(7-36)-amide; Met⁸Glu²²-GLP-1(7-36)-amide; Gly⁸Lys²²-GLP-1(7-36)-amide; Met⁸Lys²²-GLP-1(7-36)-amide; Gly⁸Arg²²-GLP-1(7-36)-amide; Val⁸Arg²²-GLP-1(7-36)-amide; Val⁸Arg²²-GLP-1(7-36)-amide; Gly⁸His²²-GLP-1(7-36)-amide; Val⁸Arg²²-GLP-1(7-36)-amide; Met⁸Arg²²-GLP-1(7-36)-amide; Val⁸His²²-GLP-1(7-36)-amide; Met⁸His²²-GLP-1(7-36)-amide; Sly⁸His²²-GLP-1(7-36)-amide; Sly⁸His²²-GLP-1(7-36)-amide; Sly⁸His
- amide; His³⁷-GLP-1(7-36)-amide; Val⁸Arg²²His³⁷-GLP-1(7-36)-amide; Met⁸Arg²²His³⁷-GLP-1(7-36)-amide; Gly⁸His³⁷-GLP-1(7-36)-amide; Val⁸His³⁷-GLP-1(7-36)-amide; Met⁸His³⁷-GLP-1(7-36)-amide; Val⁸Asp²²His³⁷-GLP-1(7-36)-amide; Met⁸Asp²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Met⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Met⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Met⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Glu²²His³⁷-GLP-1(7-36)-amide; Val⁸Clu²²His³⁷-GLP-1(7-36)-amide; Val⁸Clu²²His³⁷
- Met⁸Lys²²His³⁷-GLP-1(7-36)-amide;Gly⁸Arg²²His³⁷-GLP-1(7-36)-amide; Val⁸His²²His³⁷-GLP-1(7-36)-amide; and derivatives thereof.
 In yet another embodiment the GLP-1 agonist is selected from the group consisting of Val⁸Trp¹⁹Glu²²-GLP-1(7-37), Val⁸Glu²²Val²⁵-GLP-1(7-37), Val⁸Trp¹⁶Glu²²-GLP-1(7-37), Val⁸Leu¹⁶Glu²²-GLP-1(7-37), Val⁸Trp¹⁶Glu²²-GLP-1(7-37), Val⁸Trp¹⁶Clu²²-GL
- Val⁸Glu²²His³⁷-GLP-1(7-37), Val⁸Glu²²Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵-GLP-1(7-37), val⁸Trp¹⁶-Glu²²Val²⁵-GLP-1(7-37), val⁸-GLP-1(7-37), val

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.

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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 $X \approx P$ 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.

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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 about 10 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: <u>Nature</u>, (1960) 4736:483-485, which is hereby incorporated by reference], human insulin analogs, human insu-

- 20 lin 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-
- 25 lithocholyl) des(B30) human insulin, N^{DB29}-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 (Huma-log®), Asp^{B28} human insulin, insulin aspart (Novolog®), or a 30/70 mixture of insulin aspart and insulin aspart protamine (NovoMix®).
- 30 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

15 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 20 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 Zn²⁺ ions may be bound to each insulin 25 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 Zn²⁺ 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 Q-amino group of Lvs⁸²⁹ has a lipophilic substituent which comprises at least 6 carbon atoms.

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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

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code except Lys, Arg and Cys; Phe^{B1} may be deleted; the D-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms; and 2-4 Zn²⁺ 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 MethGH, 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.

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 formu-35 lations of the invention is from about 13 to about 15 mg/ml.

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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

15 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

25 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
 35 chelating agent where the chelating agent may be selected from salts of
 ethlenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof.

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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 mo-

25 lecular 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 pre-30 sent 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 35

embodiment of the invention the low molecular weight compound is present in a concentra-

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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

- 15 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-
- 20 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
- 25 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
- 30 lysolecithin), cationic surfactants (quarternary ammonium bases) (e.g. cetyltrimethylammonium 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
- 35 salts thereof C6-C12 (eg. oleic acid and caprylic acid), acylcarnitines and derivatives, N^αacylated 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 inventioncontain, 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;

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- 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 com-

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prises:

- 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.
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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.

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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 un-

30 derstood 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

35 (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.

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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 isreplaced 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.

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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.

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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

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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, di-

15 hydrate) 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

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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 ex-

10 periments.

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		

Table 2. The measured osmolarity of the formulations

Drop test

A droplet of each formulation is placed on a microscope slide and let to dry. The deposit is visu-5 ally 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} , $\text{Lys}^{26}(N^{r}-(\gamma-\text{Glu}(N^{\alpha}-\text{hexade-canoyl})))-\text{GLP-1}(7-37)$.

10 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.

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					12 (5 at			
(90)	25	1	0	0	needle)	0	0	0
arginin					3 (2 at			
(90)	26	2	0	0	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					16 (7 at			(1 at
(90)	32	11	5	0	needle)	1	0	needle)
glycine					1 (2 at			31 (2 at
(90)	41	9	2	0	needle)	0	0	needle)
maltose					16 (6 at			1 (5 at
(90)	35	8	7	4	needle)	0	0	needle)
laktose								31 (2 at
(90)	44	10	8	0	5	0	0	needle)

Table 3 Clogging test in NovoPen 1.5 using 30G NovoFine

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 for-

5 mulations 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

10 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

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- 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 re-

15 placements 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:

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- a. propylene glycol was observed to have no influence on the physical and chemical stability of Arg³⁴, Lys²⁶(N^ε-(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

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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:

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Disodium hydrogen phosphate, dihydrate: 1.42 mg/ml Phenol: Propylene glycol or mannitol: Water for Injection: pH: 7.90

5.5 mg/ml 13.7 or 35.9 mg/ml up to 1.0 ml.

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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.

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Example 3

Comparison of Propylene Glycol to Mannitol In Arg³⁴, Lys²⁶(Ν^ε-(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 5 and pH was adjusted to the desired pH. Arg³⁴, Lys²⁶(N^c-(y-Glu(N^a-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:

Arg³⁴, Lys²⁶(N^ε-(γ-Glu(N^α-hexadecanoyl)))-GLP-1(7-37) (6.25 mg/ml), 10 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

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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 20 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 25 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

30 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)

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Propylene glycol: 14.0 or 14.3 mg.ml

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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

Arg³⁴, Lys²⁶(N^ε-(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 Arg³⁴, Lys²⁶(N^ε-(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.
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Example 5

Clogging of needles in Lys β29 (Νε-tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations Containing Mannitol

30 **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 (Nɛ-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

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

Lys ß29 (Nɛ-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

15 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) Adjusted the pH of the solution to the desired pH and crystallized at room temperature

20 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/mł), 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 (Nɛ-tetradecanoyl) des(B30) human insulin on day 2

5 (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 Arg³⁴, Lys²⁸(N^ε-(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 β29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30 formulations containing propylene glycol

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The preparation and composition of the Lys ß29 (Nɛ-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.

- 20 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 Arg³⁴, Lys²⁶(N^ε-(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 (Nεtetradecanoyl) des(B30) human insulin and NovoMix 30-containing formulations will be simi-
- 25 lar to that observed with Arg³⁴, Lys²⁶(N^{*t*}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations.

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Claims

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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 isfrom 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.

20 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.

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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.

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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.

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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.

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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.

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17. The formulation according to claim 16, wherein said GLP-1 agonist is Arg^{34} , $\text{Lys}^{26}(N-\epsilon-(\gamma-Glu(N-\alpha-hexadecanoyl)))-GLP-1(7-37)$.

The formulation according to claim 12, wherein said GLP-1 agonist is selected from the
 group consisting of Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide,
 Val⁸-GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-36)-amide,
 Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-37), Val⁸His²²-GLP-1(7-36)-amide,
 Val⁸His²²-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.

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21. The formulation according to claim 20, wherein the insulin derivative is Lys β29 (Nεtetradecanoyl) des(B30) human insulin.

22. The formulation according to claim 20, wherein said insulin derivative is N⁰⁸²⁹-octanoyl
5 insulin.

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

10 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.

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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.

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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.
- 35 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.

5 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.

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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 15 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.

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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.

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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.

30 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 glycolcontaining formulation that must be discarded due to deposits relative to number of vials

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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

15 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.

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Abstract

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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.


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0 kia lizmera Patent- og Varemærkestyrelsen **2** 0 NOV, 2003 Mannitol Modtaget **JIG Stan** 复 FIGURE 4 that kanyte - lingende # 5 Lactose Glycine

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2 0 NOV. 2003 Modtaget Patent- og Varemærkestyre FIGURE 6

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PTOL-90A (Rev. 04/07)

	Application No.	Applicant(s)									
Office Action Summany	11/435,977	PEDERSEN ET AL.									
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	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 <u>1</u> 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 $17 M$	ay 2006.										
2a) This action is FINAL . 2b) This	action is non-final.										
3) Since this application is in condition for allowar	nce except for formal matters, pro	osecution as to the merits is									
closed in accordance with the practice under E	x parte Quayle, 1935 C.D. 11, 4	53 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 withdray	wn from consideration										
5) Claim(s) is/are allowed.											
6) Claim(s) is/are rejected.											
7) Claim(s) is/are objected to.											
8)⊠ Claim(s) <u>1-44</u> are subject to restriction and/or e	election requirement.										
Application Papers											
9) The specification is objected to by the Examine	r										
10) The drawing(s) filed on is/are: a) acc	 epted or b)∏ objected to by the l	Examiner.									
Applicant may not request that any objection to the	drawing(s) be held in abevance. See	e 37 CFR 1.85(a).									
Replacement drawing sheet(s) including the correct	ion is required if the drawing(s) is ob	jected to. See 37 CFR 1.121(d).									
11) The oath or declaration is objected to by the Ex	aminer. 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 (t).									
a) All b) Some c) None of .	s have been reactived										
2 Certified copies of the priority document	s have been received in Applicati	on No									
2. Conjos of the cortified conjos of the prior	rity documents have been received	of No									
application from the International Bureau	(PCT Rule 17.2(a))										
* See the attached detailed Office action for a list	of the certified copies not receive	d									
Attachment(s)											
 1) I Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 	4) 🔛 Interview Summary Paper No(s)/Mail Da	(PTO-413) ate.									
3) Information Disclosure Statement(s) (PTO/SB/08)	5) D Notice of Informal F	Patent Application									
Paper No(s)/Mail Date	6) 🚺 Other:										
U.S. Patent and Trademark Office PTOL-326 (Rev. 08-06) Office Ac	tion Summary Pa	rt of Paper No./Mail Date 20080526									

DETAILED ACTION

Election/Restrictions

- 1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - 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 <u>and</u> 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), Va18Glu22-GLP-1 (7-36)-amide, ValaGlu22-GLP-1(7-37), Va18Lys22-GLP-1 (7-36)-amide, Va18Arg22-GLP-1 (7-36)-amide, Va18Arg22-GLP-1 (7-37), Va18Arg22-GLP-1 (7-36)-amide, Va18Arg22-GLP-1 (7-37), Va18Arg22-GLP-1 (7-37), Va18Arg22-GLP-1 (7-36)-amide, Va18Arg22-GLP-1 (7-37), Va18Arg22-GLP-1 (7-37), Va18Arg22-GLP-1 (7-37), Va18Arg22-GLP-1 (7-37), Va18Arg22-GLP-1 (7-37), Va18Arg22-GLP-1 (7-37), Va18Arg26,34,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: Lys β 29 (N ϵ -tetradecanoyl)des(B30) human insulin and N^{L β 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. <u>All</u> 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

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.
- 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

<u>/Shelby J. Walker, Reg. No. 45,192/</u> Shelby J. Walker, Reg. No. 45,192 Novo Nordisk Inc. Customer Number 23650 (609) 987-4883



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

PTOL-90A (Rev. 04/07)

	Application No.	Applicant(s)										
Office Action Commons	11/435,977	PEDERSEN ET AL.										
Office Action Summary	Examiner	Art Unit										
	Christina Marchetti Bradley	1654										
The MAILING DATE of this communication app Period for Reply	I ne 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 <u>3</u> 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 <u>15 August 2008</u>. 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 <i>Ex parte Quayle</i>, 1935 C.D. 11, 453 O.G. 213. 												
Disposition of Claims												
 4) Claim(s) <u>1-44</u> is/are pending in the application. 4a) Of the above claim(s) <u>20-24</u> is/are withdrawn from consideration. 5) Claim(s) is/are allowed. 6) Claim(s) <u>1-19 and 25-44</u> 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. 												
Attachment(s) 1)	4) Interview Summary Paper No(s)/Mail Da 5) Notice of Informal P 6) Other:	(PTO-413) ate atent Application rt of Paper No./Mail D	ate 20081119									

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 12-18, and the species Arg^{34} , $\operatorname{Lys}^{26}(N-\epsilon-(7-Glu(N-\alpha-hexadecanoyl)))$ -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 Arg³⁴, Lys²⁶(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; Arg³⁴-GLP-1(7-37), Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide, Val⁸-GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-36)-amide, Val⁸Glu²²-GLP-1(7-37), Val⁸Lys²²-GLP-1(7-36)-amide, Val⁸Lys²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-37), Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-37), Val⁸Trp.sup.19Glu²²-GLP-1(7-37), Val⁸Glu²²Val²⁵-GLP-1(7-37), Val⁸Tvr¹⁶Glu²²-GLP-1(7-37), Val⁸Trp¹⁶Glu²²-GLP-1(7-37), Val⁸Leu¹⁶Glu²²-GLP-1(7-37), Val⁸Tyr¹⁸Glu²²-GLP-1(7-37), Val⁸Glu²²His³⁷-GLP-1(7-37), Val⁸Glu²²Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Ile³³-GLP-1(7-37), Val⁸Glu²²Val²⁵Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵-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-His⁷, Arg²⁶, Lys³⁴(N^{ε}-(γ -Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37), desamino-His⁷, Arg²⁶, Lys³⁴(N^ε-octanoyl)-GLP-1(7-37), Arg²⁶, Lys³⁴, Lys³⁸ (N^ε-(.omega.-carboxypentadecanoyl))-GLP-1(7-38), Arg^{26} , 34, $\operatorname{Lys}^{36}(N^{\epsilon}-(\gamma-\operatorname{Glu}(N^{\alpha}-\operatorname{hexadecanoyl})))-$ GLP-1 (7-36) and Arg^{34} , $\operatorname{Lys}^{26}(N^{\varepsilon}-(\gamma-\operatorname{Glu}(N^{\alpha}-\operatorname{hexadecanoyl})))-\operatorname{GLP-1}(7-37)$ (paragraphs 0038-

0040, 0064-0066). With respect to claim 19, the formulation also comprises an insulin analogue, insulin Asp^{β 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 ^{β 28}, Pro ^{β 29}-human insulin, Lys ^{β 3}, Glu ^{β 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, Lglycine, 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} , $\operatorname{Lys}^{26}(N-\varepsilon-(7-\operatorname{Glu}(N-\alpha-\operatorname{hexadecanoyl})))-\operatorname{GLP-1}(7-37)$ (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(1)(1) and § 706.02(1)(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 <u>provisional</u> 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 <u>provisional</u> 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, Lhistidine, 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 <u>provisional</u> obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

18. No claims are allowed.

 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	Art Unit			
	Christina Marchetti Bradley	1654	Page 1 of 1		

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	А	US-2006/0287221	12-2006	Knudsen et al.	514/003
*	В	US-2006/0084605	04-2006	Engelund et al.	514/012
	С	US-			
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NON-PATENT DOCUMENTS

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*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.

U.S. Patent and Trademark Office PTO-892 (Rev. 01-2001)

Notice of References Cited

Part of Paper No. 20081119

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U.S. Patent and Trademark Office

Part of Paper No.: 20081119


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torney 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

Date: July 10, 2006

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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,

Richard W. Bork, Reg. No. 36,459

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 Receipt date: 07/17/2006

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Sheet 1 of 1

FORM PTO-1449 (Rev. 2-32)	U.S. DEPART Patent and	MENT OF COMMERCE TRADEMARK OFFICE	Atty. Docket No. 6683.204-US Serial No. 11/435,977					
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A MINER BUT	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 TRANSLATION DOCUMENT NUMBER DATE COUNTRY CLASS SUBCLASS YES 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 05/20/02 03/013589 WO 1424077 05/20/02 EΡ 95/22560 02/21/95 WO 95/05848 08/23/94 WO WO 02/067989 01/08/02 92/19260 05/07/91 WO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)															
			Singh,	S	et a	L –	Aaps	Pharmscite	ch -	2003	- Vol.	4 -	Part	3-Pgs.334-342	
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EXAMINER /Christina Bradley/					DATE	CONSIDE	RED								

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.

	FILE 'CAPLU	JS	' 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)

5 S L2 (L) L3 (L) (L7 OR L8)

1 S L16 AND L1

FILE 'CAPLUS' ENTERED AT 14:38:52 ON 19 NOV 2008 L16 15664 S (PEPTIDE OR PROTEIN)(L) (L7 OR L8)

0 S (PEPTIDE OR PROTEIN) (L) (L1)

1 S (PEPTIDE OR PROTEIN) AND (L7 OR L8) AND L1

L15

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L18

L19

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

Please use the following customer number for all correspondence regarding this application. *23650* PATENT TRADEMARK OFFICE

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: 1654

Confirmation No.: 7802

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 abovecaptioned 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) Adjusted the 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 629 (Nɛ-tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 formulations containing propylene glycol

The preparation and composition of the Lys β29 (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 $\beta 29$ (N ϵ -tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 mannitol-containing formulations was similar to that observed with Arg³⁴, Lys²⁶(N ϵ -(γ -Glu(N $^{\alpha}$ -hexadecanoyl)))-GLP-1(7-37) mannitol-containing formulations, it is believed that the effect of propylene glycol on the clogging effect of Lys $\beta 29$ (N ϵ -tetradecanoyl) des(B30) human insulin and NovoMix 30-containing formulations will be similar to that observed with Arg³⁴, Lys²⁶(N ϵ -(γ -Glu(N $^{\alpha}$ -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} , $\operatorname{Lys}^{26}(N-\varepsilon-(\gamma-\operatorname{Glu}(N-\alpha-\operatorname{hexadecanoyl})))-\operatorname{GLP-1}(7-37).$

18. (Original) The formulation according to claim 12, wherein said GLP-1 agonist is selected from the group consisting of Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide, Val⁸-GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-36)-amide, V

Val⁸His²²-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 β29 (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(1)(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:

- 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;
- 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
- 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

/Shelby J. Walker, Reg. No. 45,192/

Shelby J. Walker, Reg. No. 45,192 Novo Nordisk Inc. Customer Number 23650 (609) 987-4883



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

PTOL-90A (Rev. 04/07)

	Application No.	Applicant(s)							
Office Action Summers	11/435,977	PEDERSEN ET AL.							
Office Action Summary	Examiner	Art Unit							
	CHRISTINA BRADLEY	1654							
The MAILING DATE of this communication app Period for Reply	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 <u>3</u> 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 eared patient term adjustment. 									
Status									
1) Responsive to communication(s) filed on <u>02 A</u>	<u>pril 2009</u> .								
2a)⊠ This action is FINAL . 2b)□ This	action is non-final.								
3) Since this application is in condition for allowa	nce except for formal matters, pro	psecution as to the merits is							
closed in accordance with the practice under E	Ex parte Quayle, 1935 C.D. 11, 45	53 O.G. 213.							
Disposition of Claims									
 4) Claim(s) <u>1-44</u> is/are pending in the application. 4a) Of the above claim(s) <u>20-24</u> is/are withdrawn from consideration. 5) Claim(s) is/are allowed. 6) Claim(s) <u>1-19,25-28 and 30-44</u> is/are rejected. 7) Claim(s) <u>29</u> is/are objected to. 8) Claim(s) or 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: Certified copies of the priority documents have been received. 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)		(PTO. 413)							
 1) INDICE 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) I Interview Summary Paper No(s)/Mail Da 5) Notice of Informal P 6) Other:	(PT0-413) ate Patent Application							
U.S. Patent and Trademark Office PTOL-326 (Rev. 08-06) Office Ad	ction Summary Pa	rt of Paper No./Mail Date 20090622							

DETAILED ACTION

Status of Claims

 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:

(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

A person shall be entitled to a patent unless -

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 - $(7-Glu(N-\alpha-hexadecanoyl)))$ -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; Arg³⁴-GLP-1(7-37), Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide, Val⁸-GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-36)-amide, Val⁸Glu²²-GLP-1(7-37), Val⁸Lys²²-GLP-1(7-36)-amide, Val⁸Lys²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸Arg²²-GLP-1(7-37), Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-37), Val⁸Trp.sup.19Glu²²-GLP-1(7-37), Val⁸Glu²²Val²⁵-GLP-1(7-37), Val⁸Tyr¹⁶Glu²²-GLP-1(7-37), Val⁸Trp¹⁶Glu²²-GLP-1(7-37), Val⁸Leu¹⁶Glu²²-GLP-1(7-37), Val⁸Tvr¹⁸Glu²²-GLP-1(7-37), Val⁸Glu²²His³⁷-GLP-1(7-37), Val⁸Glu²²Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Ile³³-GLP-1(7-37), Val⁸Glu²²Val²⁵Ile³³-GLP-1(7-37), Val⁸Trp¹⁶Glu²²Val²⁵-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-His⁷, Arg²⁶, Lys³⁴(N^{ε}-(γ -Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37), desamino-His⁷, Arg²⁶, Lys³⁴(N^c-octanoyl)-GLP-1(7-37), Arg²⁶, Lys³⁴, Lys³⁸ (N^c-(.omega.-carboxypentadecanoyl))-GLP-1(7-38), Arg^{26} ,34, $\operatorname{Lys}^{36}(N^{\epsilon}-(\gamma-\operatorname{Glu}(N^{\alpha}-\operatorname{hexadecanoyl})))-$ GLP-1 (7-36) and Arg^{34} , $\operatorname{Lys}^{26}(N^{\varepsilon}-(\gamma-\operatorname{Glu}(N^{\alpha}-\operatorname{hexadecanoyl})))-GLP-1$ (7-37) (paragraphs 0038-0040, 0064-0066). With respect to claim 19, the formulation also comprises an insulin analogue, insulin Asp^{β 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} , $\operatorname{Lys}^{26}(N-\varepsilon-(7-\operatorname{Glu}(N-\varepsilon)))$ 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 <u>provisional</u> 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} , $\operatorname{Lys}^{26}(N-\epsilon-(7-\operatorname{Glu}(N-\alpha-\operatorname{hexadecanoyl})))-\operatorname{GLP-1}(7-37))$. 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 <u>provisional</u> 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, Lhistidine, 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 <u>provisional</u> obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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. Any inquiry concerning this communication or earlier communications from the
examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)2729044. 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

Please use the following customer number for all correspondence regarding this application. *23650* PATENT TRADEMARK OFFICE

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: 1654

Confirmation No.: 7802

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 abovecaptioned 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 <u>peptide GLP-1</u> 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} , $\operatorname{Lys}^{26}(N-\epsilon-(\gamma-\operatorname{Glu}(N-\alpha-\operatorname{hexadecanoyl})))-\operatorname{GLP-1}(7-37)$.

18. (Original) The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide, Val⁸-GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Lys²²-GLP-1(7-36)-amide, Val⁸Glu²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-37), Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Va

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 β29 (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 about7.0 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 <u>GLP-1 agonist</u> 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 <u>GLP-1 agonist</u> 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

<u>GLP-1 agonist</u> 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
- 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.

Application No.: 11/435,977

Group Art Unit: 1654

Confirmation No.: 7802

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 <u>1-19</u>, 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

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 Injec	tion Devices			
The owner*, <u>Novo Nordisk A/S</u> , of <u>100</u> 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 <u>11/667,040</u> , filed on <u>May 3, 2007</u> , 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 .				
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent grant of any patent granted on said reference application may be shortened by any ter grant of any patent on the pending reference application," in the event that: any such patent: granted on the pending reference application, is found invalid by a court of competent ju in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of the spiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of the spiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of the spiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of the spiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration as the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to the expiration disclaimer filed prior to the expiration disclaimer filed prior	the instant application that would atent granted on said reference minal disclaimer filed prior to the bending reference application: risdiction, is statutorily disclaimed , is reissued, or is in any manner 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, gove etc.), the undersigned is empowered to act on behalf of the business/organization.	ernment agency,			
I hereby declare that all statements made herein of my own knowledge are true and that all state belief are believed to be true; and further that these statements were made with the knowledge that willdu made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States statements may jeopardize the validity of the application or any patent issued thereon.	ements made on information and false statements and the like so code and that such willful false			
2. The undersigned is an attorney or agent of record. Reg. No				
/Shelby J. Walker, Reg. No. 45,192/	November 25, 2009			
	Date			
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 be included on this form. Provide credit card information and authorization on I	should not 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.				
This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the put to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estir including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chi Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.	blic which is to file (and by the USPTO nated to take 12 minutes to complete, the individual case. Any comments on ef Information Officer, U.S. Patent and OR COMPLETED FORMS TO THIS			

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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 of 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

STATEMENT UNDER 37 CFR 3.73(b)		
Applicant/Patent Owner:	en et al.	
Application No./Patent No.: <u>11/435,977</u>	Filed/Issue Date: <u>May 17, 2006</u>	
Entitled: Propylene Glycol-Containing Peptide For	mulations 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. \checkmark the assignee of the entire right, title, and	l interest; or	
2. an assignee of less than the entire right, (The extent (by percentage) of its owner	title and interest ship interest is %)	
in the patent application/patent identified above	e by virtue of either:	
A. An assignment from the inventor(s) of the in the United States Patent and Tradema thereof is attached.	e patent application/patent identified ab rrk Office at Reel <u>018240</u> , Fram	ove. The assignment was recorded e <u>0830</u> , or for which a copy
OR B. A chain of title from the inventor(s), of the	e patent application/patent identified ab	ove, to the current assignee as follows:
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The document was recorded in th Reel, Frame _	ne United States Patent and Trademark , or for which a copy	Office at thereof is attached.
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The document was recorded in th Reel, Frame	ne United States Patent and Trademark , or for which a cop	Office at by 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 cassignee was, or concurrently is being, submit	documentary evidence of the chain of til ted for recordation pursuant to 37 CFR	tle from the original owner to the 3.11.
[NOTE: A separate copy (<i>i.e.,</i> a true copy Division in accordance with 37 CFR F 302.08]	of the original assignment document(s) Part 3, to record the assignment in the r) must be submitted to Assignment ecords of the USPTO. <u>See</u> MPEP
The undersigned (whose title is supplied below	v) is authorized to act on behalf of the a	ssignee.
/Shelby J. Walker, Re	g. No. 45,192/	November 25. 2009
Signature	e	Date
Shelby J. Walker, Re	g. No. 45.192	(609) 987-5800
Printed or Typed	d Name	Telephone Number
IP Counse Title	el	
This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain	n a benefit by the public which is to file (and by

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. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, 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.

Please use the following customer number for all correspondence regarding this application. *23650* PATENT TRADEMARK OFFICE

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: 1654

Confirmation No.: 7802

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 <u>peptide GLP-1</u> <u>agonist, a disodium phosphate dihydrate buffer</u> 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} , $\operatorname{Lys}^{26}(N-\epsilon-(\gamma-\operatorname{Glu}(N-\alpha-\operatorname{hexadecanoyl})))-\operatorname{GLP-1}(7-37)$.

18. (Original) The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of Gly⁸-GLP-1(7-36)-amide, Gly⁸-GLP-1(7-37), Val⁸-GLP-1(7-36)-amide, Val⁸-GLP-1(7-37), Val⁸Asp²²-GLP-1(7-36)-amide, Val⁸Asp²²-GLP-1(7-37), Val⁸Glu²²-GLP-1(7-37), Val⁸Lys²²-GLP-1(7-36)-amide, Val⁸Glu²²-GLP-1(7-37), Val⁸Lys²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-37), Val⁸Arg²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-37), Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-37), Val⁸His²²-GLP-1(7-36)-amide, Val⁸His²²-GLP-1(7-36)-ami

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 about7.0 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 <u>GLP-1 agonist</u> 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 <u>peptide GLP-1 agonist</u> 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 <u>GLP-1 agonist</u> 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

TERMINAL DISCLAIMER TO ORVIATE A PROVISIONAL DOUBLE PATENTING	Docket Number (Optional)			
REJECTION OVER A PENDING "REFERENCE" APPLICATION	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 Inject	tion Devices			
The owner*, <u>Novo Nordisk A/S</u> , of <u>100</u> 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 <u>11/244,497</u> , filed on <u>October 3, 2005</u> , 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, gove etc.), the undersigned is empowered to act on behalf of the business/organization.	ernment agency,			
I hereby declare that all statements made herein of my own knowledge are true and that all state belief are believed to be true; and further that these statements were made with the knowledge that wilful made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States statements may jeopardize the validity of the application or any patent issued thereon.	ements made on information and false statements and the like so s Code and that such willful false			
2. The undersigned is an attorney or agent of record. Reg. No				
/Shelby J. Walker, Reg. No. 45,192/	November 25, 2009			
Signature	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 be included on this form. Provide credit card information and authorization on I	should not 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.				
This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the put to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estir including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chi Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.	blic which is to file (and by the USPTO nated to take 12 minutes to complete, the individual case. Any comments on ef Information Officer, U.S. Patent and OR COMPLETED FORMS TO THIS			

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Application Number	Application/Co	ntrol No.	Applicant(s)/Patent u Reexamination	under
Document Code - DISQ		Internal D	ocument – DC	NOT MAIL

TERMINAL DISCLAIMER		
Date Filed : 11/25/09	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:			
Janice Ford			
two terminals approved			

U.S. Patent and Trademark Office



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

PTOL-90A (Rev. 04/07)

	Application No.	Applicant(s)
Examinor Initiated Interview Summary	11/435,977	PEDERSEN ET AL.
Examiner-initiated interview Summary	Examiner	Art Unit
	CHRISTINA BRADLEY	1654
All Participants:	Status of Application:	
(1) <u>CHRISTINA BRADLEY</u> .	(3)	
(2) <u>Shelby Walker</u> .	(4)	
Date of Interview: 24 November 2009	Time:	
Type of Interview: ☑ Telephonic ☑ Video Conference ☑ Personal (Copy given to: □ Applicant □ Applic Exhibit Shown or Demonstrated: □ Yes □ No If Yes, provide a brief description:	cant's representative)	
Part I.		
Rejection(s) discussed:		
Claims discussed: Prior art documents discussed:		
Part II.		
SUBSTANCE OF INTERVIEW DESCRIBING THE GEN	ERAL NATURE OF WHAT WA	S DISCUSSED:
The Examiner contacted Applicant to ask if the amendment to intended to be "a disodium dihydrate buffer," the former being Walker confirmed that the dihydrate was intended and that deh amending the claim to dihydrate would overcome the pending is patenting rejections would be maintained. Applicant agreed to withdrawn claims and to file terminal disclaimers. The Examine the supplemental amendment is filed.	Claim 1 to include "a disodium pho new matter and the latter being su ydrate is a typographical error. Th ejection under 35 U.S.C. § 102(e) file a supplemental amendment to er agreed that all other claim amen	sphate dehydrate buffer" was pported in the specification. Ms. ne Examiner indicated that but that the non-statutory double correct the claims and cancel adments would be entered when
Part III.		
 It is not necessary for applicant to provide a separate directly resulted in the allowance of the application. T of the interview in the Notice of Allowability. It is not necessary for applicant to provide a separate did not result in resolution of all issues. A brief summariant is the separate separate separate of the necessary for applicant to provide a separate did not result in resolution of all issues. 	record of the substance of the he examiner will provide a writ record of the substance of the ary by the examiner appears in	e interview, since the interview ten summary of the substance e interview, since the interview Part II above.
/Christina Marchetti Bradley/ Examiner, Art Unit 1654	Applicant/Applicant's Represent	ative Signature – if appropriate)
PTOL-413B (04-03) Examiner Initiated	nterview Summary	Paper No. 20091124

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 197 of 283

OK TO ENTER: /C.B./

Please use the following customer number for all correspondence regarding this application.

23650 PATENT TRADEMARK OFFICE

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: 1654

Confirmation No.: 7802

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.



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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: H	PROPYLENE GLYCOL-CO	ONTAINING PEPTIDE FORMULATIONS WHICH ARE O	PTIMAL FOR PRODUCT	ION AND
FOR USE IN INJECTION I	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. <u>PROSECUTION ON THE MERITS IS CLOSED</u>. 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 <u>THREE MONTHS</u> FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. <u>THIS STATUTORY PERIOD CANNOT BE EXTENDED</u>. 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:	If the SMALL ENTITY is shown as NO:
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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	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.

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Page 1 of 3

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 199 of 283

			PART E	B - FEE(S) TRA	NSN	AITTAL			
Complete and se	end this form, toget	her v	vith applicable	fee(s), to: <u>Mail</u> or <u>Fax</u>	Ma Co P.C Ale (57	nil Stop ISSUE mmissioner fo). Box 1450 exandria, Virgi 1)-273-2885	FEE r Pate inia 2	ents 2313-1450	
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					pape have	ers. Each additiona e its own certificate	l paper of mai	, such as an assignmen ling or transmission.	it or formal drawing, must
23650 NOVO NORD INTELLECTU/ 100 COLLEGE PRINCETON N	7590 1246 DISK, INC. AL PROPERTY DE ROAD WEST NI 08540	PAR	TMENT		I he Stat addı tran	Cer reby certify that th es Postal Service v ressed to the Mail smitted to the USP	tificate is Fee(s with suf Stop TO (57	of Mailing or Transm s) Transmittal is being ficient postage for first ISSUE FEE address 1) 273-2885, on the da	nission deposited with the United t class mail in an envelope above, or being facsimile te indicated below.
	13 005-10								(Depositor's name)
					-				(Signature)
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APPLICATION NO.	FILING DATE			FIRST NAMED INVEN	ITOR		ATTO	RNEY DOCKET NO.	CONFIRMATION NO.
11/435,977 TITLE OF INVENTIO FOR USE IN INJECTIC	05/17/2006 N: PROPYLENE GLY()N DEVICES	COL-C	CONTAINING PE	Tina Bjeldskov Pede PTIDE FORMULAT	rsen IONS	5 WHICH ARE O	PTIMA	6683.204-US AL FOR PRODUCTIC	7802 DN AND
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EXAM	AINER		ART UNIT	CLASS-SUBCLASS	3]			
BRADLEY,	CHRISTINA		1654	514-002000		1			
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an application. Confider submitting the complete	tiality is governed by 37 d d application form to the	U.S.C	2.122 and 37 CFR C. 122 Time will vary	1.14. This collection depending upon the	n or r is est indiv	imated to take 12 idual case. Any co	ne publ minutes	to complete, including s on the amount of tim	g gathering, preparing, and he you require to complete

Ins 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 Patent and Patents Patent and 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.

	ITED STATES PATE	NT AND TRADEMARK OFFICE	UNITED STATES DEPAR United States Patent and ' Address: COMMISSIONER F O. Box 1450 Alexandria, Virginia 223 www.uspto.gov	TMENT OF COMMERCE Frademark Office OR PATENTS 13-1450		
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 75	590 12/16/2009		EXAMINER			
NOVO NORDIS	K, INC.		BRADLEY, CHRISTINA			
INTELLECTUAL	PROPERTY DEPART	ART UNIT PAPER NUMBER				
100 COLLEGE RO PRINCETON, NJ	DAD WEST 08540	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.

Page 3 of 3

	Application No.	Applicant(s)									
	11/435.977	PEDERSEN ET AL.									
Notice of Allowability	Examiner	Art Unit									
	CHRISTINA BRADLEY	1654									
The MAILING DATE of this communication app All claims being allowable, PROSECUTION ON THE MERITS IS herewith (or previously mailed), a Notice of Allowance (PTOL-85 NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT R of the Office or upon petition by the applicant. See 37 CFR 1.313	ears on the cover sheet with the (OR REMAINS) CLOSED in this a) or other appropriate communicatic IGHTS. This application is subject 3 and MPEP 1308.	correspondence address pplication. If not included on will be mailed in due course. THIS to withdrawal from issue at the initiative									
1. X This communication is responsive to the after-final amend	ment filed 11/25/2009.										
2. 🔀 The allowed claim(s) is/are <u>1-9,13-18,28 and 30-44</u> .											
 3. Acknowledgment is made of a claim for foreign priority u a) All b) □ Some* c) □ None of the: 1. A Certified copies of the priority documents have 2. □ Certified copies of the priority documents have 	 3. X Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) X All b) Some* c) None of the: 1. X 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 do	cuments 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") mu	st be submitted.										
(a) ☐ including changes required by the Notice of Draftsper	son's Patent Drawing Review(PTC	0-948) attached									
1) 🔲 hereto or 2) 🔲 to Paper No./Mail Date											
(b) ∐ including changes required by the attached Examiner' Paper No./Mail Date	s Amendment / Comment or in the	Office action of									
Identifying indicia such as the application number (see 37 CFR 1 each sheet. Replacement sheet(s) should be labeled as such in	l.84(c)) should be written on the draw the header according to 37 CFR 1.121	rings in the front (not the back) of I(d).									
 DEPOSIT OF and/or INFORMATION about the depo attached Examiner's comment regarding REQUIREMENT 	ISIT OF BIOLOGICAL MATERIAL	must be submitted. Note the CAL MATERIAL.									
Attachment(s) 1. Notice of References Cited (PTO-892) 2. Notice of Draftnerson's Patent Drawing Review (PTO 948)	5. 🗌 Notice of Informal	Patent Application									
	Paper No./Mail D	y (PTO-413), ate									
3. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date	7. 🛛 Examiner's Ameno	dment/Comment									
4. Examiner's Comment Regarding Requirement for Deposit of Biological Material	8. 🛛 Examiner's Staten	nent of Reasons for Allowance									
/Anish_Gupta/											
Primary Examiner, Art Unit 1654											
U.S. Patent and Trademark Office PTOL-37 (Rev. 08-06) N	otice of Allowability	Part of Paper No./Mail Date 20091201									

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 202 of 283

EXAMINER'S AMENDMENT

 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- l(7-38) analogues thereof and derivatives of any of these." and insert --Arg³⁴GLP- l(7-37), Arg^{26,34}Lys³⁶GLP- l(7-36), Arg²⁶GLP-l(7-37), and Gly⁸Arg^{26,34}Glu³⁷Lys³⁸GLP- l(7-38) and derivatives of any of these." therefor.

28. (Currently Amended) A method of preparing a <u>GLP-1 agonistpeptide</u>-formulation suitable for use in an injection device, said method comprising preparing a formulation containing <u>a</u> <u>GLP-1 agonist,peptide and</u> propylene glycol, <u>a disodium phosphate dihydrate buffer</u>, 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 <u>GLP-1 agonistpeptide</u>, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

Application/Control Number: 11/435,977 Art Unit: 1654

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

b) preparing a second solution by dissolving the <u>GLP-1 agonistpeptide</u> 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 most 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.

Application/Control Number: 11/435,977 Art Unit: 1654

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/

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Receipt date: 07/17/2006

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Sheet	1	of	1
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	FORM PTO-1449 (Rev. 2-32)		U.S. DEPART PATENT AND	MENT OF COMMERCI	E Atty. Docket No. 6683.204	-US	Serial No. 11/435,977					
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			2002/0151467	12/21/00	Leung, F.K.							
			5206219	11/25/91	Applied Analytical Industries, INC							
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				FOREIGN	PATENT DOCUMENTS							
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		OTHER I	OCUMENTS (Includin	g Author, Title, Date, I	ertinent Pages, Etc.)		
		Singh, S et	: al - Aaps Ph	armscitech -	2003 - Vol.	4 - Part 3	-Pgs.334-342
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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

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11435977 - GAU: 1654

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FORM PTO-1449 (Rev. 2-32)	U.S. DEPART Patent and	MENT OF COMMERCE	Atty. Docket No. 6683.204	-US	Serial No. 11/4	35,977			
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7 2006	Use several sheets if necessary))	Filing Date May 17, 2000	6	Group 1646	Group 1646			
JUL		U.S. PAT	ENT DOCUMENTS						
MINER ANT	DOCUMENT NUMBER	DATE	NAME	CLASS	FILING SUBCLASS IF APPRO		CLASS SUBCLASS		G DATE
	2002/0151467	12/31/00	Leung, F.K.			10/17/	2002		
	5206219	11/25/91	Applied Analytical Industries, INC						
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	2005/046716	11/12/04	WO						
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	99/16417	10/01/97	WO						
	03/013589	05/20/02	WO						
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95/05848	08/23/94	WO			
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92/19260	05/07/91	WO			
OTHER :	DOCUMENTS (Including /	Author, Title, Date, Perting	ent Pages, Etc.)		
Singh, S e	t al - Aaps Phar	rmscitech - 200	3 - Vol. 4 - P	art 3-Pgs.334-34	2
	95/22560 95/05848 02/067989 92/19260 OTHER Singh, S e	95/22560 02/21/95 95/05848 08/23/94 02/067989 01/08/02 92/19260 05/07/91 OTHER DOCUMENTS (Including / Singh, S et al - Aaps Phan	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, Perting Singh, S et al - Aaps Pharmscitech - 200	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 - P	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.334-34

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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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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	ł	
This is a Req Request for C 1995, or to an	uest for Continu ontinued Examina y design applicati	ed Examination (RCE) on. The Ins	ation (RCE) under 3 practice under 37 Cl struction Sheet for thi	B7 CFR 1.114 of the FR 1.114 does not ap is form is located at V	above-identified application oply to any utility or plant applie VWW.USPTO.GOV	cation filed	l prior to June 8,
		S	UBMISSION REQ	UIRED UNDER 37	CFR 1.114		
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Suspensi (Period c	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	Other						
FEES							
The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed. Image: 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 Applica	Patent Practitioner Signature Applicant Signature						

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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.

Attorney Docket No.: 6683.204-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al.

Application No.: 11/435,977

Filed: May 17, 2006

Conf. No.: 7802

Group Art Unit: 1654

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:

Attorney Docket No.: 6683.204-US

U.S. Application No. 11/435,977

				Application No.	11/435,977
INFORMATION DISCLOSURE				Filing Date	May 17, 2006
	STATEMENT BY API	PLICAP	NT	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	Т

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.	Т
		Non-Final Office Action mailed December 9, 2009 in U.S. Application No. 12/184,531 filed August 1, 2008 by Mortensen <i>et al.</i>	

EXAMINER	DATE	
SIGNATURE	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: H	PROPYLENE GLYCOL-CO	ONTAINING PEPTIDE FORMULATIONS WHICH ARE O	PTIMAL FOR PRODUCT	ION AND
FOR USE IN INJECTION I	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. <u>PROSECUTION ON THE MERITS IS CLOSED</u>. 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 <u>THREE MONTHS</u> FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. <u>THIS STATUTORY PERIOD CANNOT BE EXTENDED</u>. 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:	If the SMALL ENTITY is shown as NO:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.	A. Pay TOTAL FEE(S) DUE shown above, or
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	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.

Page 1 of 3

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL									
Complete and se	nd this form, toget	her with applicable	e fee(s), to: <u>Mail</u> Ma Co P.(Alc or <u>Fax</u> (57	Mail Stop ISSUE FEE Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 (571)-273-2885					
INSTRUCTIONS: This appropriate. All further indicated unless correct maintenance fee notifica	form should be used f correspondence includin ed below or directed oth tions.	for transmitting the ISSU ng the Patent, advance on nerwise in Block 1, by (a	UE FEE and PUBLICAT rders and notification of r a) specifying a new corre	ION FEE (if required). E maintenance fees will be spondence address; and/or	Blocks 1 through 5 sho mailed to the current c (b) indicating a separ	ould be completed where orrespondence address as ate "FEE ADDRESS" for			
CURRENT CORRESPOND	ENCE ADDRESS (Note: Use BI	ock 1 for any change of address)	Not Fee pap	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 bars its our contributor for mailing or transmission.					
23650 NOVO NORD INTELLECTUA 100 COLLEGE PRINCETON, N	7590 04/06 VISK, INC. AL PROPERTY DE ROAD WEST VJ 08540	/2010 PARTMENT	I he Stat add trar	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	ATTO	RNEY DOCKET NO.	CONFIRMATION NO.			
11/435,977	05/17/2006	•	Tina Bjeldskov Pedersen		6683.204-US	7802			
APPLN. TYPE	N DEVICES	ISSUE FEE DIE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATEDUE			
nonprovisional	NO	\$1510	\$300	\$0	\$1810	07/06/2010			
EXAN	IINER	ART UNIT	CLASS-SUBCLASS]					
BRADLEY.	CHRISTINA	1654	514-002000]					
1. Change of correspond CFR 1.363). Change of corresp Address form PTO/SJ "Fee Address" ind PTO/SB/47; Rev 03-(Number is required.	ence address or indicatio condence address (or Cha B/122) attached. lication (or "Fee Address 20 or more recent) attach	n of "Fee Address" (37 nge of Correspondence " Indication form eed. Use of a Customer	2. For printing on the patent front page, list 1 (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 (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. 2						
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 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)									
4. The fellowing fraction		(······				
 4a. The following fee(s) are submitted: Issue Fee Publication Fee (No small entity discount permitted) Advance Order - # of Copies 			 b. 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 Sta	tus (from status indicate is SMALL ENTITY stati	d above) 1s. See 37 CFR 1.27.	b . Applicant is no lon	ger claiming SMALL ENT	TITY status. See 37 CFI	R 1.27(g)(2).			
NOTE: The Issue Fee an interest as shown by the	d Publication Fee (if req records of the United Sta	uired) will not be accepte tes Patent and Trademark	d from anyone other than COffice.	the applicant; a registered a	ttorney or agent; or the	assignee or other party in			
Authorized Signature				Date					
Typed or printed name				Registration No.					
This collection of inform an application. Confiden submitting the complete this form and/or suggest Box 1450, Alexandria, V Alexandria, Virginia 223	nation is required by 37 C tiality is governed by 35 d application form to the ions for reducing this bu /irginia 22313-1450. DC 113-1450.	FR 1.311. The informatic U.S.C. 122 and 37 CFR USPTO. Time will vary rden, should be sent to th NOT SEND FEES OR	on is required to obtain or 1.14. This collection is es depending upon the indi e Chief Information Offic COMPLETED FORMS T	retain a benefit by the publ timated to take 12 minutes vidual case. Any comment er, U.S. Patent and Traden O THIS ADDRESS. SENI	ic which is to file (and to complete, including s on the amount of tim nark Office, U.S. Depar D TO: Commissioner fo	by the USPTO to process) gathering, preparing, and e you require to complete tment of Commerce, P.O. r Patents, P.O. Box 1450,			

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UNITED STATES PATENT AND TRADEMARK OFFICE 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			EXAMINER					
NOVO NORDIS	K, INC.	BRADLEY, CHRISTINA						
INTELLECTUAL	PROPERTY DEPART	ART UNIT	PAPER NUMBER					
100 COLLEGE RO PRINCETON, NJ	DAD WEST 08540	1654 DATE MAILED: 04/06/201	0					

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.

Page 3 of 3
	Application No.	Applicant(s)							
	11/435,977	PEDERSEN ET AL.							
Notice of Allowability	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. X This communication is responsive to the RCE filed 3/16/20	<u>010</u> .								
2. 🔀 The allowed claim(s) is/are <u>1-9,13-18,28 and 30-44</u> .									
 3. X 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. X Certified copies of the priority documents have been received. 									
2. 🗌 Certified copies of the priority documents have	e been received in Application No.	·							
3. Copies of the certified copies of the priority do	cuments have been received in this	s national stage application from the							
International Bureau (PCT Rule 17.2(a)).									
* Certified copies not received:									
Applicant has THREE MONTHS FROM THE "MAILING DATE" noted below. Failure to timely comply will result in ABANDONN THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.	of this communication to file a repl /IENT of this application.	y complying with the requirements							
4. A SUBSTITUTE OATH OR DECLARATION must be subm INFORMAL PATENT APPLICATION (PTO-152) which giv	nitted. Note the attached EXAMINE es reason(s) why the oath or decla	R'S AMENDMENT or NOTICE OF ration is deficient.							
5. CORRECTED DRAWINGS (as "replacement sheets") mu	st be submitted.								
(a) ∐ including changes required by the Notice of Draftspers	son's Patent Drawing Review(PTC	D-948) attached							
1) L hereto or 2) L to Paper No./Mail Date									
(b) I including changes required by the attached Examiner Paper No./Mail Date	s Amendment / Comment or in the	Office action of							
Identifying indicia such as the application number (see 37 CFR 1 each sheet. Replacement sheet(s) should be labeled as such in	l.84(c)) should be written on the draw the header according to 37 CFR 1.12	vings in the front (not the back) of 1(d).							
 DEPOSIT OF and/or INFORMATION about the depo attached Examiner's comment regarding REQUIREMENT 	Sit of BIOLOGICAL MATERIAL	must be submitted. Note the CAL 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 Summar	y (PTO-413),							
3. ☑ Information Disclosure Statements (PTO/SB/08), Paper No /Mail Date 3/16/2010	7. C Examiner's Ameno	dment/Comment							
 4. Examiner's Comment Regarding Requirement for Deposit of Biological Material 	8. 🔲 Examiner's Staten	nent of Reasons for Allowance							
/Christina Marchetti Bradley/									
Examiner, Art Unit 1654									
U.S. Patent and Trademark Office PTOL-37 (Rev. 08-06) N	otice of Allowability	Part of Paper No./Mail Date 20100326							

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.

Any inquiry concerning this communication or earlier communications from the
examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)2729044. 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 Application/Control Number: 11/435,977 Art Unit: 1654

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

EXAL (DED

Lau

Attorney Docket No.: 6683.204-US

DOGLE CENTE NUE OFFE

U.S. Application No. 11/435,977

		~ ~ ~ ~ ~ ~		Application No.	11/435,977
	INFORMATION DISC	LOSUI	KE	Filing Date	May 17, 2006
	STATEMENT BY API	PLICAP	NT	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

INITIALS	No.	Number –Kind Code ^{((f known)}	Date MM-DD-YYYY	Applicant of Cited Document	Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code ^(ff 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.	Т
/C.B./		Non-Final Office Action mailed December 9, 2009 in U.S. Application No. 12/184,531 filed August 1, 2008 by Mortensen <i>et al.</i>	

EXAMINER SIGNATURE /Christina Bradley/ DATE 03/26/2010
--

Doc code: RCEX Doc description: Request for Continued Examination (RCE)

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL									
			(Submitte	d 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 Req Request for C 1995, or to an	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								
		S	UBMISSION REC	QUIRED UNDER 37	7 CFR 1.114				
Note: If the Ri in which they entered, appli	CE is proper, any were filed unless cant must reques	previously f applicant ins t non-entry c	iled unentered ame structs otherwise. If of such amendment	ndments and amendn applicant does not wi (s).	nents enclosed with the RCI ish to have any previously fi	E will be ente led unentered	red in the order I amendment(s)		
Previousl submissio	y submitted. If a fi on even if this box	nal Office a	ction is outstanding, ked.	, any amendments file	ed after the final Office action	n may be con	sidered as a		
□ Co	nsider the argum	ents in the A	oppeal Brief or Repl	y Brief previously filed	l on				
	ner								
X Enclosed									
Ar	nendment/Reply								
🗙 Inf	ormation Disclosu	ire Statemer	nt (IDS)						
Aff	idavit(s)/ Declarat	tion(s)							
Ot	her								
			MIS	SCELLANEOUS					
Suspensi (Period o	on of action on th of suspension sha	e above-ide Ill not excee	ntified application is d 3 months; Fee un	requested under 37 der 37 CFR 1.17(i) re	CFR 1.103(c) for a period c quired)	of months			
Other									
FEES									
The RC The Dire Deposit	The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed. Image: The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 141447								
	,	SIGNATUF	RE OF APPLICAN	IT, ATTORNEY, OF	R AGENT REQUIRED				
🗙 Patent	Practitioner Sign	ature							
Applic	ant Signature								

EFS - Web 2.1.15

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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)

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL									
			(Submitte	d 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 Req Request for C 1995, or to an	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								
		S	UBMISSION REC	QUIRED UNDER 37	7 CFR 1.114				
Note: If the Ri in which they entered, appli	CE is proper, any were filed unless cant must reques	previously f applicant ins t non-entry o	iled unentered ame structs otherwise. If of such amendment	ndments and amendn applicant does not wi (s).	nents enclosed with the RCl ish to have any previously fi	E will be ente led unentered	red in the order I amendment(s)		
Previously submission	y submitted. If a fi on even if this box	nal Office a	ction is outstanding, ked.	, any amendments file	ed after the final Office action	n may be con	sidered as a		
□ Co	nsider the argum	ents in the A	ppeal Brief or Repl	y Brief previously filed	l on				
🗌 🗌 Otl	ner								
X Enclosed									
Ar	nendment/Reply								
🗙 Inf	ormation Disclosu	ire Statemer	nt (IDS)						
Aff	idavit(s)/ Declarat	tion(s)							
🗌 🗌 Ot	her								
			MIS	SCELLANEOUS					
Suspensi (Period o	on of action on th of suspension sha	e above-ide Ill not excee	ntified application is d 3 months; Fee un	s requested under 37 der 37 CFR 1.17(i) re	CFR 1.103(c) for a period c quired)	of months			
Other									
FEES									
The RCI The Dire Deposit	The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed. Image: State of the Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 141447								
	;	SIGNATUR		IT, ATTORNEY, OF	R AGENT REQUIRED				
🗙 Patent	Practitioner Sign	ature							
Applic	ant Signature								

EFS - Web 2.1.15

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.

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.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al.

Application No.: 11/435,977

Filed: May 17, 2006

Confirmation No.: 7802

Group Art Unit: 1654

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:

	DEODMATION DISC	TOCIO		Application No.	11/435,977
	INFORMATION DISC		KE	Filing Date	May 17, 2006
	STATEMENT BY API	PLICA		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 ^(ff 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.				
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EXAMINER	Cite	DOCUMENT NUMBER	Publication Date	NAME of Patentee or	Pages, Columns, Lines Where Relevant	Т
INITIALS	NO.	Number -Kind Code	07.04.06	Applicant of Cited Document	Passages of Relevant Figures Appear	-
		w0 96/20005	07-04-96	Novo Nordisk A/S		
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		WO 99/43341	09-02-99	Novo Nordisk A/S		
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		WO 00/15224	03-23-00	Eli Lilly & Co.		
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EXAMINER SIGNATURE				DATE CONSIDERED		

			-	Application No.	11/435,977
	INFORMATION DISC	LOSURI	£	Filing Date	May 17, 2006
	STATEMENT BY APP.	LICAN	Ľ	Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	3	Atty. Docket No.	6683.204-US

			FOREIGN PATI	ENT DOCUMENTS		
EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number – Kind Code ^(if Inown)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	Т
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EXAMINER SIGNATURE				DATE CONSIDERED		

Application No. 11/435,977 INFORMATION DISCLOSURE Filing Date May 17, 2006 STATEMENT BY APPLICANT Pedersen et al. Applicant Art Unit 1654 Examiner Name: Bradley, Christina Sheet 3 of 3 Atty. Docket No. 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.	Т
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EXAMINER SIGNATURE DATE CONSIDERED 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 Novo Nordisk Inc. Customer Number 23650 (609) 987-4883

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al.

Conf. No.: 7802

Application No.: 11/435,977

Filed: May 17, 2006

Examiner: Bradley, Christina

Group Art Unit: 1654

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, <u>AMENDMENT</u> 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 <u>5</u> Forms PTO-1449 sheet for consideration by the Examiner in accordance with 37 C.F.R. §§ 1.56, 1.97, and 1.98:

U.S. Application No. 11/435,977

				Application No.	11/435,977
INFORMATION DISCLOSU		RE	Filing Date	May 17, 2006	
STATEMENT BY APPLICANT				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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				Application No.	11/435,977
	INFORMATION DISC	LOSU	RE	Filing Date	May 17, 2006
	STATEMENT BY API	PLICA	NT	Applicant	Pedersen et al.
				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.	Т
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	INFORMATION DISCLOSURE STATEMENT BY APPLICANT			RE	Filing Date	May 17, 2006	
	STAT	TEMENT BY APP.	LICA	INT .	Applicant	Pedersen et al.	
					Art Unit	1654	
					Examiner Name:	Bradley, Christina	
Sheet	3		of	5	Atty. Docket No.	6683.204-US	
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		INVENTORS: M	ADK	ISSEN ET AI	ATTORNEV Γ	$\mathbf{OCKET NO} (6555, 210 \text{ US})$	
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		INVENTORS: M	ARK	USSEN ET AL.	(ATTORNEY D	OCKET NO. 6555.210-US)	
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EXAMINER	DATE	
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				Application No.	11/435,977
	INFORMATION DISC		KE.	Filing Date	May 17, 2006
	STATEMENT BY API	PLICA	NT	Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet 4 of 5		5	Atty. Docket No.	6683.204-US	

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FINAL OFFICE ACTION IN 11/290,635, FILED , INVENTORS: JUUL- MORTENSEN ET AL. (ATTORNEY DOCKET NO. 6689.204-US) SENT SEPTEMBER 5, 2007	

EXAMINER	DATE	
SIGNATURE	CONSIDERED	

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				Application No.	11/435,977
	INFORMATION DISC	LOSUI	ξΕ	Filing Date	May 17, 2006
	STATEMENT BY API	PLICAP	NT	Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	5	of	5	Atty. Docket No.	6683.204-US

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EXAMINER	DATE	
SIGNATURE	CONSIDERED	
	CONDIDINED	

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 (609) 987-5800

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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 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

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. <u>PROSECUTION ON THE MERITS IS CLOSED</u>. 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 <u>THREE MONTHS</u> FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. <u>THIS</u> <u>STATUTORY PERIOD CANNOT BE EXTENDED</u>. 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:	If the SMALL ENTITY is shown as NO:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.	A. Pay TOTAL FEE(S) DUE shown above, or
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	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.

Page 1 of 3

PTOL-85 (Rev. 02/11)

		PART I	B - FEE(S) TRAN	SMITTAL			
Complete and ser	nd this form, toget	her with applicable	e fee(s), to: <u>Mail</u>	Mail Stop ISSUE Commissioner fo P.O. Box 1450 Alexandria, Virg 571)-273-2885	E FEE or Patent ginia 223	ts 13-1450	
INSTRUCTIONS: This appropriate. All further of indicated unless correcte maintenance fee notificat	form should be used f correspondence includin d below or directed oth	for transmitting the ISSI ng the Patent, advance o nerwise in Block 1, by (UE FEE and PUBLIC. rders and notification (a) specifying a new co	ATION FEE (if requ of maintenance fees v rrespondence address	uired). Bloo will be mai ; and/or (b	cks 1 through 5 sho iled to the current c b) indicating a separa	ould be completed where orrespondence address as ate "FEE ADDRESS" for
23650 NOVO NORD INTELLECTUA 100 COLLEGE I PRINCETON, N	NNCE ADDRESS (Note: Use BI 7590 03/14 ISK, INC. L PROPERTY DE ROAD WEST J 08540	ock 1 for any change of address) /2011 PARTMENT		Note: A certificate of Fee(s) Transmittal. Th papers. Each additiona have its own certificate Cert hereby certify that th States Postal Service v Iddressed to the Mai ransmitted to the USP	mailing ca iis certifica al paper, su e of mailing rtificate of nis Fee(s) T with suffici il Stop ISS 2TO (571) 2	an only be used for the cannot be used for uch as an assignment g or transmission. * Mailing or Transm Fransmittal is being ient postage for first SUE FEE address a 273-2885, on the date	domestic mailings of the r any other accompanying t or formal drawing, must ission deposited with the United class mail in an envelope bove, or being facsimile e indicated below.
							(Depositor's name)
			·				(Signature) (Date)
APPLICATION NO.	FILING DATE		FIRST NAMED INVENT	ÖR	ATTORN	EY DOCKET NO.	CONFIRMATION NO.
11/435 977	05/17/2006		Tina Bieldskov Peder	sen	66	83 204-US	7802
USE IN INJECTION DE	VICES						
APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE D	JE PREV. PAID ISSU	JE FEE 1	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1510	\$300	\$0		\$1810	06/14/2011
EXAM	INER	ART UNIT	CLASS-SUBCLASS				
BRADLEY, C	CHRISTINA	1654	514-002000				
1. Change of corresponde CFR 1.363). Change of corresponde Address form PTO/SB TO/SB/47; Rev 03-0 Number is required.	nce address or indicatio ondence address (or Cha /122) attached. cation (or "Fee Address 2 or more recent) attach	n of "Fee Address" (37 nge of Correspondence " Indication form ed. U se of a Customer	2. For printing on the constraint of the same of the constraint of the same of the constraint of the same of the s	te patent front page, li o to 3 registered pater latively, ngle firm (having as a or agent) and the nam attorneys or agents. If be printed.	ist nt attorneys a member a nes of up to no name is	s 1 a 2 s 3	
3. ASSIGNEE NAME A PLEASE NOTE: Unl recordation as set fort (A) NAME OF ASSIC	ND RESIDENCE DAT/ ess an assignee is ident i in 37 CFR 3.11. Comj iNEE	A TO BE PRINTED ON ified below, no assignee oletion of this form is NO	THE PATENT (print or data will appear on th T a substitute for filing (B) RESIDENCE: (C	type) e patent. If an assign an assignment. ITY and STATE OR C	nee is ident COUNTRY	tified below, the doc	cument has been filed for
Please check the appropri	ate assignee category or	categories (will not be p	rinted on the patent):		orporation	or other private grou	p entity 🖵 Government
4a. The following fee(s) a Issue Fee Publication Fee (N Advance Order - #	re submitted: o small entity discount J of Copies	4) permitted)	 b. Payment of Fee(s): (I A check is enclose Payment by credit The Director is her overpayment, to D 	Please first reapply and d. card. Form PTO-2038 eby authorized to chau eposit Account Numb	ny previou 8 is attache rge the requer	usly paid issue fee sh ed. uired fee(s), any defi (enclose an	town above) ciency, or credit any extra copy of this form).
5. Change in Entity Stat	us (from status indicate s SMALL ENTITY state	d above) 18. See 37 CFR 1.27.	b . Applicant is no	longer claiming SMA	LL ENTIT	TY status. See 37 CFI	R 1.27(g)(2).
NOTE: The Issue Fee and interest as shown by the r	l Publication Fee (if req ecords of the United Sta	uired) will not be accepte tes Patent and Trademark	d from anyone other the office.	an the applicant; a regi	istered atto	orney or agent; or the	assignee or other party in
Authorized Signature				Date			
Typed or printed name	·			Registration N	No		
This collection of informa	ation is required by 37 C	FR 1.311. The information U.S.C. 122 and 37 CFR	on is required to obtain 1.14. This collection is	or retain a benefit by t	the public y	which is to file (and l	by the USPTO to process)

O 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.

	ted States Pate	NT AND TRADEMARK OFFICE	UNITED STATES DEPAR United States Patent and Address: COMMISSIONER F P.O. Box 1450 Alexandria, Virginia 223 www.uspto.gov	TMENT OF COMMERCE Trademark Office OR PATENTS 313-1450
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 75	90 03/14/2011		EXAM	fINER
NOVO NORDIS	K, INC. PROPERTY DEPART	BRADLEY,	CHRISTINA	
100 COLLEGE RO	DAD WEST		ART UNIT	PAPER NUMBER
PRINCETON, NJ	08540		1654	
			DATE MAILED: 03/14/201	.1

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.

	Application No.	Applicant(s)					
		· · · · · · · · · · · · · · · · · · ·					
Notice of Allowability	11/435,977	PEDERSEN ET AL.					
	∟xaminer						
	CHRISTINA BRADLEY	1654					
The MAU INC DATE of this communication	are on the cover chect with the						
The MAILING DATE of this communication apportunity of the MAILING DATE of this communication apportunity of the All claims being allowable, PROSECUTION ON THE MERITS IS herewith (or previously mailed), a Notice of Allowance (PTOL-85) NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT R of the Office or upon petition by the applicant. See 37 CFR 1.313	corrections on the cover sheet with the (OR REMAINS) CLOSED in this a or other appropriate communication IGHTS. This application is subject and MPEP 1308.	<i>correspondence address</i> pplication. If not included on will be mailed in due course. THIS to withdrawal from issue at the initiative					
1. X This communication is responsive to the RCE filed 06/25/2	<u>2010</u> .						
2. X The allowed claim(s) is/are <u>1-9,13-18,28 and 30-44</u> .							
3. Acknowledgment is made of a claim for foreign priority un	nder 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	e been received.						
2. Certified copies of the priority documents have	e been received in Application No	·					
3. Copies of the certified copies of the priority do	cuments have been received in this	s 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") mus	5. CORRECTED DRAWINGS (as "replacement sheets") must be submitted.						
(a) 🔲 including changes required by the Notice of Draftspers	son's Patent Drawing Review (PTC	D-948) attached					
1)							
(b) ☐ including changes required by the attached Examiner' Paper No./Mail Date	s Amendment / Comment or in the	Office action of					
Identifying indicia such as the application number (see 37 CFR 1 each sheet. Replacement sheet(s) should be labeled as such in t	.84(c)) should be written on the draw he header according to 37 CFR 1.121	rings in the front (not the back) of I(d).					
6. DEPOSIT OF and/or INFORMATION about the depo attached Examiner's comment regarding REQUIREMENT	sit of BIOLOGICAL MATERIAL	must be submitted. Note the CAL 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 Summar Paper No./Mail D	y (PTO-413), ate					
3. Information Disclosure Statements (PTO/SB/08), Paper No /Mail Date See Continuation Sheet	7. 🗌 Examiner's Ameno	dment/Comment					
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material	8. 🛛 Examiner's Staten	nent of Reasons for Allowance					
	9. Other						
/Christina Marchetti Bradley/ Primary Examiner, Art Unit 1654							
U.S. Patent and Trademark Office		.					
PTOL-37 (Rev. 08-06) No.	otice of Allowability	Part of Paper No./Mail Date 20110303					

Continuation Sheet (PTOL-37)

Application No. 11/435,977

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.

Application/Control Number: 11/435,977 Art Unit: 1654

 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

US Application No.: 11/435,977 Attorney Docket No.: 6683.204-US

			Application No.	11/435,977	
	INFORMATION DISC	CLOSUI	KE.	Filing Date	May 17, 2006
	STATEMENT BY API	PLICA	NT	Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	3	Atty. Docket No.	6683.204-US

			U.S. PATENI	DOCUMENTS	
EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code ^(ff Intown)	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 PAT	ENT DOCUMENTS		
EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number – Kind Code ^(ff Incown)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	Т
		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./

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 245 of 283

US Application No.: 11/435,977 Attorney Docket No.: 6683.204-US Filing Date: May 17, 2006 Page 3 of 5

	INFORMATION DISC STATEMENT BY APP	LOSUR LICAN	E	Application No. Filing Date Applicant Art Unit	11/435,977 May 17, 2006 Pedersen et al. 1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	3	Atty. Docket No.	6683.204-US

			FOREIGN PAT	ENT DOCUMENTS		
EXAMINER INITIALS	Cite No	DOCUMENT NUMBER	Publication Date	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant	Т
Internet States	110.	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	

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US Application No.: 11/435,977 Attorney Docket No.: 6683.204-US

Filing Date: May 17, 2006 Page 4 of 5

			-	Application No.	11/435,977
	INFORMATION DISC.	LOSUR	C .	Filing Date	May 17, 2006
	STATEMENT BY APP	LICAN		Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	3	of	3	Atty. Docket No.	6683.204-US

			NON PATENT LITERATU	<u>RE DOCUMENTS</u>					
	Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the symposium, catalog, etc.), date, pages(s), volume-issue number(s	article (when appropriat), publisher, city and/or (e), title of the item (book, magazine, journal, serial, country where published.	Т			
****	****		3ERENDSEN, 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 Pharmaceuti	cal Sciences, 199	97, Vol. 86, No. 7, pages 768-773				
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			GOOD, N. E., www.FERMANTES.COM	*****					
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			LARSEN, P. J. ET AL., Diabetes 2001, Vol.	50, pages 2530-2	2539				
			MALENDOWICH ET AL., Journal of Molec	cular Medicine, 2	2002, Vol. 10, No. 3, pages 327-331				
	***************************************	0000000000	MESSER, W. S., Vasopressin and Oxytocin, 2000						
			OL H. ET AL., PDA Journal of Pharmaceutic	cal Science & Te	chnology, 1995, Vol. 49, No. 6.				
			pages 289-293						
		00000000000000000	RUDINGER I. Peptide Hormones, 1976, pa	<u>1965.1-7</u>					
			SENDEROFF, R. I. ET AL., J. Pharm. Sci., 1	998, Vol. 87, Pa	rt 2, pages 183-189				
			SIGMA. Custom Peptide Synthesis, 2004, pa	ges 1-2. http://ww	ww.SIGMA-	<u> </u>			
			GENOSYS.COM/PEPTIDE_DESIGN.ASP	8-0 1 - ,					
			SMILEK, D. E. ET AL., Proceedings of the N	National Academ	y of Sciences of USA, 1991, Vol.				
			88, pages 9055-9057	at and Industrial	Dhamma conticols 1005 Vol 21	<u> </u>			
		000000000000000000000000000000000000000	No. 13, pages 1303-1311						
		00000000000	VOET, D. ET AL., Biochemistry, 1995, 2 nd E	Edition, pages 23	5-241				
1	EXAMINER			DATE					
	SIGNATURE		/Christina Bradley/	CONSIDERED	03/03/2011				

US Application No.: 11/435,977	Filing Date: May 17, 2006
Attorney Docket No.: 6683.204-US	Page 5 of 5

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

Attorney Docket No.: 6683.204-US

U.S. Application No. 11/435,977

				Application No.	11/435,977
	INFORMATION DISC	CLOSUI	RE	Filing Date	May 17, 2006
STATEMENT BY APPLICANT				Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	1	of	5	Atty. Docket No.	6683.204-US

			U.S. PATENI	DOCUMENTS	
EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code ^{((f 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.	
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		5652216	7/29/1997	KORNFELT ET	
		6133229	Oct-2000	GIBSON ET AL.	
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EXAMINER INITIALS	Cite No.	DOCUMENT NUMBER Number –Kind Code ^(f known)	Publication Date MM-DD-YYYY	NAME of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	Т
		WO0152937	7/26/2001	MINIMED INC.		
		EP1344533	9/17/2003	NATIMMUNE A/S		
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		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	
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 249 of 283

U.S. Application No. 11/435,977

		~ ~ ~ ~ ~		Application No.	11/435,977
	INFORMATION DISC	CLOSUI	XE	Filing Date	May 17, 2006
	STATEMENT BY API	PLICA	NT	Applicant	Pedersen et al.
				Art Unit	1654
				Examiner Name:	Bradley, Christina
Sheet	2	of	5	Atty. Docket No.	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.	Т
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		ENTRY FOR GLYCERIN IN DRUGS.COM (WWW.DRUGS.COM/PPA/GLYCERIN-	
		GLYCEROL.HTML), PRINTED 08/04/2009	
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		EUROPE-STRASBOURG	
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SIGNATURE	CONSIDERED	

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PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 250 of 283

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Attorney Docket No.: 6683.204-US

U.S. Application No. 11/435,977

				11/435,977		
	INFO	ORMATION DISCLOSURE	Filing Date	May 17, 2006		
	STA	TEMENT BY APPLICANT	Applicant	Pedersen et al.		
			Art Unit	1654		
			Examiner Name:	Bradley, Christina		
Sheet	3	of 5	Atty. Docket No.	6683.204-US		
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		SKOVGAARD ET AL., "USING EVOI	LUTIONARY IN	FORMATION AND		
		ANCESTRAL SEQUENCES TO UNDI	ERSTAND THE	SEQUENCE-FUNCTION		
		RELATIONSHIP IN GLP-1 AGONIST	S," J. MOL. BIO.	, 2006, VOL. 363, PAGES		
		977-988				
		TSOKA ET AL, SELECTIVE FLOCCU	JLATION ANDS	PRECIPITATION FOR THE		
	IMPROVEMENT OF VIRUS-LIKE PARTICLE RECOVERY FROM YEAST					
		HOMOGENATE, BIOTECHNOL PRO	G. VOL. 16(4), P	PP. 661-7 (2000)		
	NON EINAL OFFICE ACTION IN 10/185 023 EILED JUNE 27 2002 INVENTORS					
		FLINK ET AL (ATTORNEY DOCKE	Г NO 6358 500-І	US) SENT MARCH 10, 2006		
	TEINK ET AL. (ATTOKNET DOCKET NO. 0558.500-05) SENT MARCH 10, 2000					
		NON-FINAL OFFICE ACTION IN 10/2	185,923, FILED J	UNE 27, 2002, INVENTORS:		
		FLINK ET AL. (ATTORNEY DOCKE)	Г NO. 6358.500-U	US) SENT OCTOBER 9, 2007		
		NON-FINAL OFFICE ACTION IN 11/2	786,095, FILED A	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				
		NON-FINAL OFFICE ACTION IN 10/	719 601 EII ED M	NOVEMBER 21 2003		
		$\mathbf{NVFNTORS} \cdot \mathbf{MARKUSSENFT} \Delta \mathbf{I} = \mathbf{I}$	ATTORNEY DO	CKET NO 6555 200-US)		
		SENT MARCH 4 2005		CRET 110. 0555.200-055		
		5LITT MILLION 7, 2005				
		NON-FINAL OFFICE ACTION IN 11/2	220,266, FILED S	SEPTEMBER 6, 2005,		
		INVENTORS: MARKUSSEN ET AL. (ATTORNEY DO	DCKET NO. 6555.210-US)		
		SENT SEPTEMBER 14, 2006				
		NON-FINAL OFFICE ACTION IN 11/2	220,266, FILED S	SEPTEMBER 6, 2005,		
		INVENTORS: MARKUSSEN ET AL. (ATTORNEY DO	DCKET NO. 6555.210-US)		
		SENT FEBRUARY 11, 2008				
		NON-FINAL OFFICE ACTION IN 11/	220.266 FILED 8	SEPTEMBER 6 2005		
		INVENTORS: MARKUSSEN ET AL	ATTORNEY DO	OCKET NO 6555 210-US)		
		SENT OCTOBER 1 2007				
		SIATE OCTOBIA 1, 2007				

EXAMINER	DATE	
SIGNATURE	CONSIDERED	

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Attorney Docket No.: 6683.204-US

U.S. Application No. 11/435,977

				Application No. 11/435,977				
	INF	ORMATION DISCLOSU	RE	Filing Date	May 17, 2006			
	STATEMENT BY APPLICANT			Applicant	Pedersen et al.			
				Art Unit	1654			
				Examiner Name:	Bradley, Christina			
Sheet	4	of	5	Atty. Docket No.	6683.204-US			
		NON	PATENT LITERAT	URE DOCUMENTS	•			
		NON FINAL OFFICE	ACTION IN 11/	200.634 EU ED I	NOVEMBER 30, 2005			
		INVENTORS: JUUL-MORTENSEN ET AL. (ATTORNEY DOCKET NO. 6702.204- US) SENT JUNE 30, 2008						
		NON-FINAL OFFICE INVENTORS: JUUL-M US) SENT NOVEMBE	ACTION IN 11/2 MORTENSEN E ER 9, 2007	290,634, FILED 1 T AL. (ATTORN	NOVEMBER 30, 2005, EY DOCKET NO. 6702.204-			
		NON-FINAL OFFICE ACTION IN 11/290,635, FILED NOVEMBER 30, 2005, INVENTORS: JUUL-MORTENSEN ET AL. (ATTORNEY DOCKET NO. 6689.204- US) SENT FEBRUARY 2, 2007						
		NON-FINAL OFFICE INVENTORS: JUUL-M US) SENT FEBRUAR	ACTION IN 11/2 MORTENSEN E ⁷ Y 2, 2007	290,635, FILED I T AL. (ATTORN	NOVEMBER 30, 2005, NEY DOCKET NO. 6689.204-			
		NON-FINAL OFFICE ACTION IN 11/365,274, FILED MARCH 1, 2006, INVENTORS: SCIILEIN ET AL. (ATTORNEY DOCKET NO. 6711.204-US) SENT AUGUST 20, 2007						
		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 ACTIO FLINK ET AL. (ATTO 2006	ON IN 10/185,92 DRNEY DOCKE	23, FILED JUNE Γ NO. 6358.500-1	27, 2002, INVENTORS: US) SENT DECEMBER 12,			
		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 FLINK ET AL. (ATTO	ON IN 10/185,92 PRNEY DOCKE	23, FILED JUNE2 T NO. 6358.500-1	27, 2002, INVENTORS: US) SENT JUNE 30, 2008			
		FINAL OFFICE ACTIO MORTENSEN ET AL. SEPTEMBER 5, 2007	ON IN 11/290,63 . (ATTORNEY E	5, FILED , INV DOCKET NO. 66	ENTORS: JUUL- 89.204-US) SENT			

SIGNATURE CONSIDERED	EXAMINER	DATE	
	SIGNATURE	CONSIDERED	

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Attorney Docket No.: 6683.204-US

U.S. Application No. 11/435,977

				Application No.	11/435,977
	INFORMATION DISC	LOSUI	KE	Filing Date	May 17, 2006
	STATEMENT BY APP	LICA	N'I'	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	
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	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 DATE SIGNATURE /Christina Bradley/ CONSIDERED (03/03/2011
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./

Doc code: RCEX Doc description: Request for Continued Examination (RCE)

	REQ	UEST FC		D EXAMINATIC	N(RCE)TRANSMIT	TAL		
			(Submitte	d 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 Req Request for C 1995, or to an	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							
		S	UBMISSION REC	QUIRED UNDER 37	7 CFR 1.114			
Note: If the Ri in which they entered, appli	CE is proper, any were filed unless cant must reques	previously f applicant ins t non-entry o	iled unentered ame structs otherwise. If of such amendment	ndments and amendn applicant does not wi (s).	nents enclosed with the RCl ish to have any previously fi	E will be ente led unentered	red in the order I amendment(s)	
Previously submission	y submitted. If a fi on even if this box	nal Office a	ction is outstanding, ked.	, any amendments file	ed after the final Office action	n may be con	sidered as a	
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Suspensi (Period o	on of action on th of suspension sha	e above-ide Ill not excee	ntified application is d 3 months; Fee un	s requested under 37 der 37 CFR 1.17(i) re	CFR 1.103(c) for a period c quired)	of months		
Other								
				FEES				
The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed. Image: 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 Sign	ature						
Applic	ant Signature							

EFS - Web 2.1.15

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.

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.

Application No.: 11/435,977

Filed: May 17, 2006

Group Art Unit: 1654

Conf. No.: 7802

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 <u>two</u> Forms PTO-1449 sheets for consideration by the Examiner in accordance with 37 C.F.R. §§ 1.56, 1.97, and 1.98:

			-	Application No.	11/435,977
	INFORMATION DISC	LOSURI	E.	Filing Date	May 17, 2006
	STATEMENT BY APP.	LICAN	L	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	Т
		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 DISC	LOSURI	E	Application No. Filing Date	11/435,977 May 17, 2006
STATEMENT BY APPLICANT				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.	Т
		REMINGTON'S PHARMACEUTICAL SCIENCES, MACK PUBLISHING COMPANY, 16 TH EDITION 1980 CHAPTER 79 PAGE 1406	
		PLUMER'S PRINCIPLES & PRACTICE OF INTRAVENOUS THERAPY, 2006, EDITION 8, PAGES 124-128	
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		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 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 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. <u>PROSECUTION ON THE MERITS IS CLOSED</u>. 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 <u>THREE MONTHS</u> FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. <u>THIS</u> <u>STATUTORY PERIOD CANNOT BE EXTENDED</u>. 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:	If the SMALL ENTITY is shown as NO:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.	A. Pay TOTAL FEE(S) DUE shown above, or
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	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.

Page 1 of 3

PTOL-85 (Rev. 02/11)

Complete and se	nd this form, toget	PART I	B - FEE(S) TRAN e fee(s), to: <u>Mail</u>	SMITTAL Mail Stop ISSU Commissioner f P.O. Boy, 1450	E FEE or Pat) ents		
			or <u>Fax</u>	Alexandria, Vir (571)-273-2885	ginia 2	22313-1450		
INSTRUCTIONS: This appropriate. All further indicated unless correct	form should be used f correspondence includir ed below or directed oth	for transmitting the ISS ng the Patent, advance of nerwise in Block 1, by (UE FEE and PUBLIC rders and notification a) specifying a new co	CATION FEE (if req of maintenance fees prrespondence addres	uired). will be s; and/c	Blocks 1 through 5 sho mailed to the current c or (b) indicating a separ	ould be completed where orrespondence address as ate "FEE ADDRESS" for	
23650 NOVO NORD	ENCE ADDRESS (Note: Use Bi 7590 07/19 VISK, INC.	ock 1 for any change of address) /2011		Note: A certificate o Fee(s) Transmittal. T papers. Each addition have its own certifica Co I hereby certify that i	f mailin his certi nal pape te of ma e rtificat this Fee	g can only be used for ficate cannot be used fo r, such as an assignmen uiling or transmission. e of Mailing or Transm (s) Transmittal is being	domestic mailings of the r any other accompanying t or formal drawing, must hission deposited with the United	
100 COLLEGE PRINCETON, N	ROAD WEST 108540	PARIMENI		States Postal Service addressed to the Ma transmitted to the US	with su ul Stop PTO (57	fficient postage for first ISSUE FEE address a 71) 273-2885, on the dat	class mail in an envelope bove, or being facsimile e indicated below.	
							(Depositor's name) (Signature)	
-							(Date)	
APPLICATION NO.	FILING DATE		FIRST NAMED INVEN	TOR	ATTO	ORNEY DOCKET NO.	CONFIRMATION NO.	
TITLE OF INVENTION USE IN INJECTION DF	I: PROPYLENE GLYCO EVICES	DL-CONTAINING PEPT	IDE FORMULATION	IS WHICH ARE OPT	TIMAL I	FOR PRODUCTION AN	ND FOR	
APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE D	UE PREV. PAID ISS	UE FEE	TOTAL FEE(S) DUE	DATE DUE	
nonprovisional	NO	\$1510	\$300	\$0		\$1810	10/19/2011	
EXAN	IINER	ART UNIT	CLASS-SUBCLASS	CLASS-SUBCLASS				
BRADLEY,	CHRISTINA	1654	514-007200					
 Change of correspond CFR 1.363). Change of corresp Address form PTO/SD "Fee Address" ind PTO/SB/47; Rev 03- Number is required. 	ence address or indicatio ondence address (or Cha B/122) attached. lication (or "Fee Address 2 or more recent) attach	n of "Fee Address" (37 nge of Correspondence " Indication form ed. Use of a Customer	 For printing on t the names of u or agents OR, alter the name of a s registered attorney registered patent listed, no name wil 	he patent front page, p to 3 registered pate natively, single firm (having as or agent) and the na attorneys or agents. I Il be printed.	list ent attor a meml mes of u f no nar	neys 1 ber a 2 np to 3		
3. ASSIGNEE NAME A PLEASE NOTE: Un recordation as set fort (A) NAME OF ASSI	ND RESIDENCE DATA less an assignee is ident h in 37 CFR 3.11. Comp GNEE	A TO BE PRINTED ON ified below, no assignee oletion of this form is NC	THE PATENT (print o data will appear on th T a substitute for filing (B) RESIDENCE: (C	r type) ne patent. If an assig an assignment. TTY and STATE OR	gnee is i COUN	dentified below, the doo	cument has been filed for	
Please check the appropr	iate assignee category or	categories (will not be p	rinted on the patent):		Corporat	tion or other private grou	p entity 🔲 Government	
4a. The following fee(s) Issue Fee Publication Fee () Advance Order - # 	are submitted: No small entity discount <u>r</u> # of Copies	4 permitted)	 b. Payment of Fee(s): (A check is enclos Payment by credi The Director is he overpayment, to D 	Please first reapply ed. t card. Form PTO-202 reby authorized to ch Deposit Account Num	any pre 38 is atta arge the ber	viously paid issue fee sl uched. required fee(s), any defi (enclose an	hown above) ciency, or credit any extra copy of this form).	
5. Change in Entity Sta	tus (from status indicate as SMALL ENTITY state	d above) 1s. See 37 CFR 1.27.	b. Applicant is no	longer claiming SMA	ALL EN	TITY status. See 37 CF	R 1.27(g)(2).	
NOTE: The Issue Fee an interest as shown by the	d Publication Fee (if req records of the United Sta	uired) will not be accepte ttes Patent and Trademarl	ed from anyone other th k Office.	an the applicant; a re	gistered	attorney or agent; or the	assignee or other party in	
Authorized Signature				Date				
Typed or printed nam	e			Registration	No			
This collection of inform an application. Confiden	nation is required by 37 C tiality is governed by 35 d application form to the	CFR 1.311. The informati U.S.C. 122 and 37 CFR	on is required to obtain 1.14. This collection i	or retain a benefit by s estimated to take 12	the put minute	blic which is to file (and s to complete, including	by the USPTO to process) gathering, preparing, and	

O to process) 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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	ted States Pate	ENT AND TRADEMARK OFFICE	UNITED STATES DEPAR United States Patent and Address: COMMISSIONER F P.O. Box 1450 Alexandria, Virginia 223 www.usplo.gov	TMENT OF COMMERCE Trademark Office OR PATENTS 913-1450	
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 75	90 07/19/2011		EXAM	IINER	
NOVO NORDIS	K, INC. PROPERTY DEPART	- MENT	BRADLEY, CHRISTINA		
100 COLLEGE RO	DAD WEST		ART UNIT	PAPER NUMBER	
PRINCETON, NJ	08540		1654		
			DATE MAILED: 07/19/201	1	

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.

	Application No.	Applicant(s)					
		·					
Notice of Allowability	11/435,977	PEDERSEN ET AL.					
	CHRISTINA BRADLEY	1654					
The MAILING DATE of this communication appr All claims being allowable, PROSECUTION ON THE MERITS IS herewith (or previously mailed), a Notice of Allowance (PTOL-85) NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT R of the Office or upon petition by the applicant. See 37 CFR 1.313 1. This communication is responsive to the RCE filed 06/10/2	ears on the cover sheet with the (OR REMAINS) CLOSED in this a or other appropriate communication IGHTS. This application is subject and MPEP 1308.	<i>correspondence address</i> pplication. If not included on will be mailed in due course. THIS to withdrawal from issue at the initiative					
2. 🔀 The allowed claim(s) is/are <u>1-9,13-18,28 and 30-44</u> .							
 3. X Acknowledgment is made of a claim for foreign priority up a) X All b) Some*c) None of the: 1. X Certified copies of the priority documents have 2. Certified copies of the priority documents have 3. Copies of the certified copies of the priority documents have 	nder 35 U.S.C. § 119(a)-(d) or (f). e been received. e been received in Application No						
International Bureau (PCT Bule 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 subm INFORMAL PATENT APPLICATION (PTO-152) which give	itted. Note the attached EXAMINE es reason(s) why the oath or decla	R'S AMENDMENT or NOTICE OF ration is deficient.					
5. CORRECTED DRAWINGS (as "replacement sheets") must	st be submitted.						
(a)	son's Patent Drawing Review (PTC	D-948) attached					
1) hereto or 2) to Paper No./Mail Date							
(b) ☐ including changes required by the attached Examiner' Paper No./Mail Date	s Amendment / Comment or in the	Office action of					
Identifying indicia such as the application number (see 37 CFR 1 each sheet. Replacement sheet(s) should be labeled as such in t	.84(c)) should be written on the draw he header according to 37 CFR 1.12	rings in the front (not the back) of I(d).					
6. DEPOSIT OF and/or INFORMATION about the depo attached Examiner's comment regarding REQUIREMENT	sit of BIOLOGICAL MATERIAL FOR THE DEPOSIT OF BIOLOGI	must be submitted. Note the CAL MATERIAL.					
Attachment(s)	5 Notice of Informal	Patent Application					
2. Notice of Draftperson's Patent Drawing Review (PTO-948)	6. Interview Summar	v (PTO-413).					
	Paper No./Mail D	ate					
3. ⊠ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>06/10/2011</u>	7. Examiner's Ameno	dment/Comment					
4. Li Examiner's Comment Regarding Requirement for Deposit of Biological Material	8. ⊠ Examiner's Staten	nent of Heasons for Allowance					
	9. Other						
/Christina Marchetti Bradley/ Primary Examiner, Art Unit 1654							
U.S. Patent and Trademark Office PTOL-37 (Rev. 08-06)	otice of Allowability	Part of Paper No./Mail Date 20110616					

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.

Any inquiry concerning this communication or earlier communications from the
examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)2729044. 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 Application/Control Number: 11/435,977 Art Unit: 1654

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

Receipt date: 06/10/2011 US Application No.: 11/435,977 Attorney Docket No.:6683.204-US

	INFORMATION DISCI	LOSURI	R.	Application No.	11/435,977
	STATEMENT RV ADD	LICAN	C r	Filing Date	May 17, 2006
	STATEMENT DI AFF.	LICAN	L	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	Т
/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		

Receipt date: 06/10/2011

US Application No.: 11/435,977 Attorney Docket No.:6683.204-US

			-	Application No.	11/435,977
	INFORMATION DISC		E	Filing Date	May 17, 2006
STATEMENT BY APPLICANT				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.	Т
		REMINGTON'S PHARMACEUTICAL SCIENCES, MACK PUBLISHING COMPANY, 16 TH	
/U.B./		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, 3 RD EDITION, 1997, PAGES 17-18	
/C.B./		UNITED STATES PHARMACOPOEIA, 24 TH 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, 18 TH 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	

EXAN	MINER		/Christina Bra	adlev/	1			DATE		06/16/0011
SIGN	ATURE	.	YZ]		- 7	UTD - I I		CONSIDERED		00/10/2011
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/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)

	REG	UEST FO			N(RCE)TRANSM	ITTAL				
			(Submitte	ed 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. Pederse	en	1	Examiner Name	C. Bradley	I	P			
This is a Req Request for C 1995, or to an	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									
		S	SUBMISSION RE	QUIRED UNDER 37	7 CFR 1.114					
Note: If the Ro in which they entered, appli	CE is proper, any were filed unless cant must reque	/ previously f applicant in st non-entry	filed unentered ame structs otherwise. I of such amendmen	endments and amendn f applicant does not wi t(s).	nents enclosed with the lish to have any previousl	RCE will be ente ly filed unentered	red in the order I amendment(s)			
Previously submissio	y submitted. If a on even if this bo	final Office a x is not chec	ction is outstanding ked.), any amendments file	ed after the final Office ac	ction may be con	sidered as a			
□ Co	nsider the argun	nents in the A	Appeal Brief or Rep	ly Brief previously filed	l on					
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X Enclosed										
🗌 An	nendment/Reply									
🗙 Inf	ormation Disclos	ure Stateme	nt (IDS)							
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Suspensi (Period o	on of action on t of suspension sh	he above-ide all not excee	entified application i ed 3 months; Fee ur	s requested under 37 nder 37 CFR 1.17(i) re	CFR 1.103(c) for a period quired)	od of months				
Other										
				FEES						
The RCI The Dire Deposit	 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 									
		SIGNATU	RE OF APPLICAI	NT, ATTORNEY, OF	R AGENT REQUIRED					
X Patent	Practitioner Sig ant Signature	nature								

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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. <u>PROSECUTION ON THE MERITS IS CLOSED</u>. 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 <u>THREE MONTHS</u> FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. <u>THIS</u> <u>STATUTORY PERIOD CANNOT BE EXTENDED</u>. 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:	If the SMALL ENTITY is shown as NO:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.	A. Pay TOTAL FEE(S) DUE shown above, or
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	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.

Page 1 of 3

PTOL-85 (Rev. 02/11)

PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 271 of 283

		PART I	R - FEE(S) TRAN	ISM	ITTAL		
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INSTRUCTIONS: This appropriate. All further indicated unless correcte maintenance fee notificat	form should be used f correspondence includined below or directed other itions	for transmitting the ISSU of the Patent, advance of herwise in Block 1, by (UE FEE and PUBLIC orders and notification a) specifying a new co	CATIO of m orresp	ON FEE (if required). I aintenance fees will be bondence address; and/or	Blocks 1 through 5 sh mailed to the current r (b) indicating a sepa	ould be completed where correspondence address as rate "FEE ADDRESS" for
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.			
							(Signature)
							(Date)
APPLICATION NO.	FILING DATE		FIRST NAMED INVEN	TOR	ATTO	RNEY DOCKET NO.	CONFIRMATION NO.
11/435 977	05/17/2006		Tina Bieldskov Peder	rsen		6683 204-US	7802
TITLE OF INVENTION USE IN INJECTION DE	: PROPYLENE GLYCC VICES	DL-CONTAINING PEPT	IDE FORMULATION	IS WI	HICH ARE OPTIMAL F	FOR PRODUCTION A	ND FOR
APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE D	DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1740	\$300		\$0	\$2040	02/01/2012
EXAM	INER	ART UNIT	CLASS-SUBCLASS	3			
BRADLEY, O	CHRISTINA	1654	514-007200				
Change of corresponde CFR 1.363). Change of corresponder Address form PTO/SE "Fee Address" indi PTO/SB/47; Rev 03-0 Number is required.	ence address or indicatio ondence address (or Cha \$/122) attached. ication (or "Fee Address 2 or more recent) attach	n of "Fee Address" (37 nge of Correspondence " Indication form ed. Use of a Customer	 For printing on t the names of u or agents OR, alter the name of a s registered attorney registered patent listed, no name will 	the pa ip to inative single or ag attor il be p	tent front page, list 3 registered patent attorn ely, firm (having as a memb gent) and the names of u neys or agents. If no nan vrinted.	neys 1 per a 2 p to ne is 3	
3. ASSIGNEE NAME A) PLEASE NOTE: Unl recordation as set forth (A) NAME OF ASSIG	ND RESIDENCE DAT/ ess an assignee is ident i n 37 CFR 3.11. Comp GNEE	A TO BE PRINTED ON f ified below, no assignee oletion of this form is NO	THE PATENT (print o data will appear on th T a substitute for filing (B) RESIDENCE: (C	or type he pa g an a CITY	e) tent. If an assignee is ic ssignment. and STATE OR COUNT	dentified below, the dc TRY)	cument has been filed for
Please check the appropriation 4a. The following fee(s) a Issue Fee Publication Fee (N Advance Order - #	tate assignee category or are submitted: to small entity discount p of Copies	categories (will not be p 4 permitted)	 b. Payment of Fee(s): (A check is enclos Payment by credi The Director is he overpayment, to I 	Pleas sed. it card ereby Depos	Individual Corporations for the corporation of the	ion or other private gro viously paid issue fee s ched. required fee(s), any def (enclose ar	in the second se
 Change in Entity State a. Applicant claims 	t us (from status indicate s SMALL ENTITY statu	d above) 1s. See 37 CFR 1.27.	b. Applicant is no	o long	er claiming SMALL EN	TITY status. See 37 CF	FR 1.27(g)(2).
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Typed or printed name	e				Registration No.		
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O to process) an application. Confidentiality is governed by 35 UCFX F1.51.1 the information is related to collar of testimate do 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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PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 272 of 283

	ted States Pate	NT AND TRADEMARK OFFICE	UNITED STATES DEPAR United States Patent and Address: COMMISSIONER F P.O. Box 1450 Alexandria, Virginia 223 www.uspto.gov	TMENT OF COMMERCE Trademark Office OR PATENTS 913-1450	
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 75	90 11/01/2011		EXAMINER		
NOVO NORDIS	K, INC. PROPERTY DEPART	MENT	BRADLEY, CHRISTINA		
100 COLLEGE RO	DAD WEST		ART UNIT	PAPER NUMBER	
PRINCETON, NJ	08540		1654		
			DATE MAILED: 11/01/201	1	

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.

	Application No.	Applicant(s)
Notice of Allowability	Examiner	Art Unit
-		
	CHRISTINA BRADLEY	1654
The MAILING DATE of this communication appe All claims being allowable, PROSECUTION ON THE MERITS IS herewith (or previously mailed), a Notice of Allowance (PTOL-85) NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RI of the Office or upon petition by the applicant. See 37 CFR 1.313	ars on the cover sheet with the c (OR REMAINS) CLOSED in this ap or other appropriate communicatior GHTS. This application is subject t and MPEP 1308.	orrespondence address plication. If not included n will be mailed in due course. THIS o withdrawal from issue at the initiative
1. X This communication is responsive to the RCE filed 09/15/20	<u>11</u> .	
2. An election was made by the applicant in response to a rest requirement and election have been incorporated into this action.	riction requirement set forth during t	the interview on; the restriction
3. ⊠ The allowed claim(s) is/are <u>1-9,13-18,28 and 30-44</u> .		
 4. X Acknowledgment is made of a claim for foreign priority unde a) X All b) □ Some* c) □ None of the: 	r 35 U.S.C. § 119(a)-(d) or (f).	
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 doo	cuments 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 noted below. Failure to timely comply will result in ABANDONM THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.	of this communication to file a reply ENT of this application.	complying with the requirements
5. A SUBSTITUTE OATH OR DECLARATION must be submit INFORMAL PATENT APPLICATION (PTO-152) which give	ted. Note the attached EXAMINER's reason(s) why the oath or declara	S AMENDMENT or NOTICE OF ation is deficient.
6.	be submitted.	
(a) 🔲 including changes required by the Notice of Draftspers	on'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 Paper No./Mail Date	Amendment / Comment or in the C	Office action of
Identifying indicia such as the application number (see 37 CFR 1. each sheet. Replacement sheet(s) should be labeled as such in th	84(c)) should be written on the drawine header according to 37 CFR 1.121(ngs in the front (not the back) of /d).
7. DEPOSIT OF and/or INFORMATION about the deposit of B attached Examiner's comment regarding REQUIREMENT FC	IOLOGICAL MATERIAL must be su R THE DEPOSIT OF BIOLOGICAL	ubmitted. Note the _ MATERIAL.
Attachment(s)	5 🗖 Notice of Informal E	Patent Application
2 Notice of Draftnerson's Patent Drawing Beview (PTO-948)	6. Interview Summary	
	Paper No./Mail Da	te
 Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 09/15/2011 	7. 🗌 Examiner's Amendi	ment/Comment
4. Examiner's Comment Regarding Requirement for Deposit	8. 🛛 Examiner's Stateme	ent of Reasons for Allowance
	9. 🔲 Other	
/Christina Bradley/ Primary Examiner, Art Unit 1654		
U.S. Patent and Trademark Office PTOL-37 (Rev. 03-11) No	tice of Allowability	Part of Paper No./Mail Date 20111021

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.

Application/Control Number: 11/435,977 Art Unit: 1654

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

Beceiptdate: 09/15/2011

Doc description: Information Disclosure Statement (IDS) Filed

11435977 - GAL:001654

mation Disclosure Statement (IDS) Filed U.S. Patent and Trademark Office; U.S. DePARTIMENT 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.

Application Number 11435977 Filing Date 2006-05-17 INFORMATION DISCLOSURE First Named Inventor Tina B. Pedersen STATEMENT BY APPLICANT Art Unit 1654 (Not for submission under 37 CFR 1.99) Examiner Name C. Bradley Attorney Docket Number 6683.204-US

U.S.PATENTS Remove										
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue D	ate	Name of Patentee or Applicant of cited Document		Pages,Columns,Lines where Relevant Passages or Relev Figures Appear		e vant
/C.B./	1	4468346		1984-08	-28	Paul et al.				
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/C.B./	1	20040156835	A1	2004-08	-12	Imoto et al.				
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Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	/ i	Kind Code⁴	Publication Date	Name of Patentee Applicant of cited Document	e or	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T⁵
/C.B./	1	2000-510813	JP			2000-08-22	GENETICS INSTIT	UTE	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	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B./ EFS Web 2.1.17

Receipt date: 09/15/2011

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number		11435977	11435977 - GAU: 1654
Filing Date		2006-05-17	
First Named Inventor Tina E		3. Pedersen	
Art Unit		1654	
Examiner Name C. Br		adley	
Attorney Docket Numb	er	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.I	₿, ∦ 1	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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PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 278 of 283

Receipt date: 09/15/2011

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number		11435977	11435977 - GAU: 1654
Filing Date		2006-05-17	
First Named Inventor	Tina E	3. Pedersen	
Art Unit		1654	
Examiner Name	C. Bra	adley	
Attorney Docket Number		6683.204-US	

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/C.B./	1	ELI LILLY & CO., HUMALOG LISPRO INJECTION, USP PRODUCT INFORMATION DATED FEBRUARY 11, 2010	
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PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 279 of 283

Receipt date: 09/15/2011 Application Number Filing Date

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number		11435977	11435977 - GAU: 1654
Filing Date		2006-05-17	
First Named Inventor Tina E		3. Pedersen	
Art Unit		1654	
Examiner Name C. Bra		adley	
Attorney Docket Numb	er	6683.204-US	

/C.B./	10	MARTIN A. ET AL., PHYSICAL PHARMACY; PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES, 1983, 3RD EDITION, PG. 232	
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/C.B./	12	SIGMA PRODUCT INFORMATION ON GLY-GLY BUFFER DATED MARCH 16, 2010	
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/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	
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PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1003, p. 280 of 283

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 E	. Pedersen		
	Art Unit		1654		
	Examiner Name	C. Bra	adley		
	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.					
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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.

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Receipt date: 09/15/2011	Application Number		11435977	11435977	- GAU: 1654
	Filing Date		2006-05-17		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	First Named Inventor	Tina E	. Pedersen		
	Art Unit		1654		
	Examiner Name	C. Bra	adley		
	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 here	with.			
X A certification sta	atement 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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UNITED STATES PATENT AND TRADEMARK OFFICE

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 NOVO NORDISK, INC. INTELLECTUAL PROPERTY DEPARTMENT 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).

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APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Tina Bjeldskov Pedersen, Smorum, DENMARK; Claude Bonde, Lyngby, DENMARK; Dorthe Kot Engelund, Holte, DENMARK;

IR103 (Rev. 10/09)