Exhibit A

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

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

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

31 Claims, 7 Drawing Sheets

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FIGURE 1

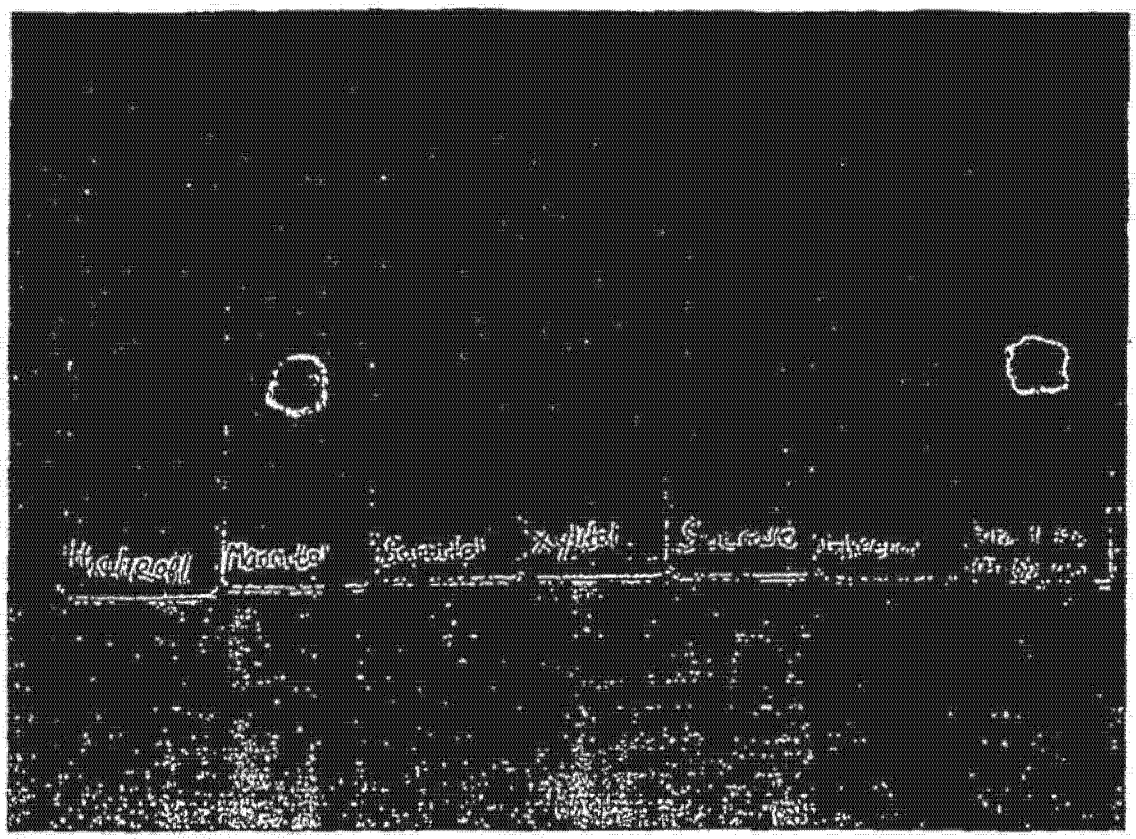
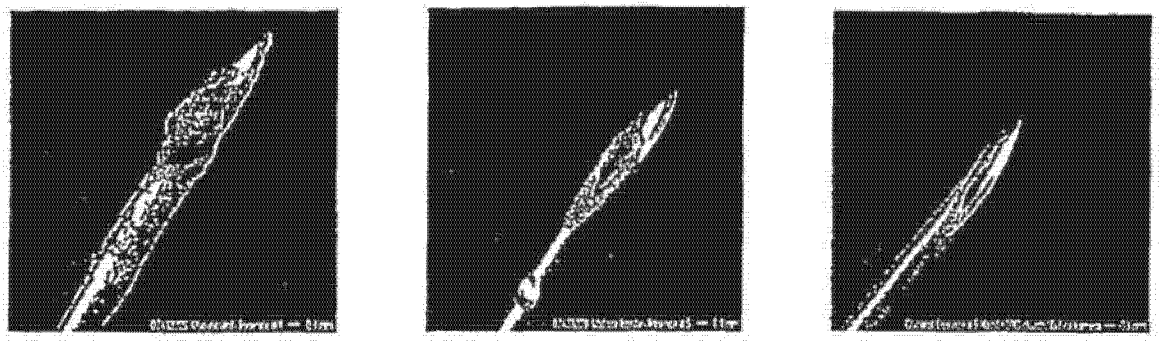


FIGURE 2

FIGURE 3



Myo-inositol Maltose Glycerol

FIGURE 4

Glycine Lactose Mannitol

FIGURE 5

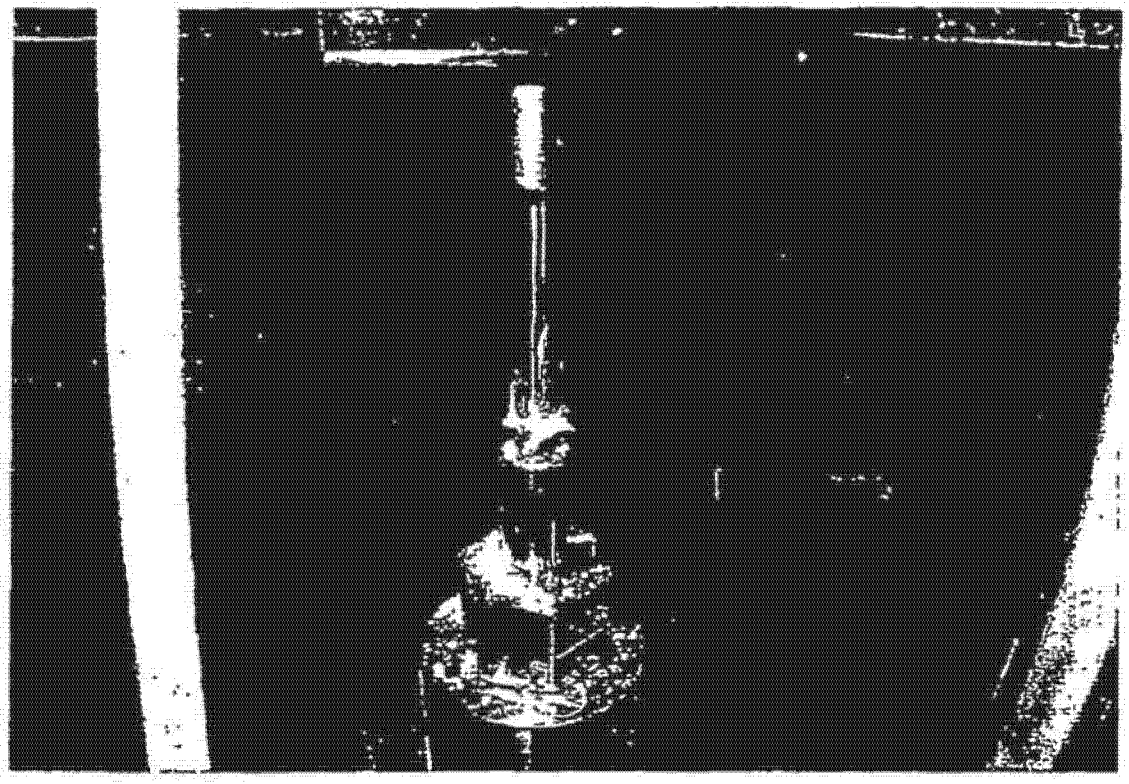


FIGURE 6

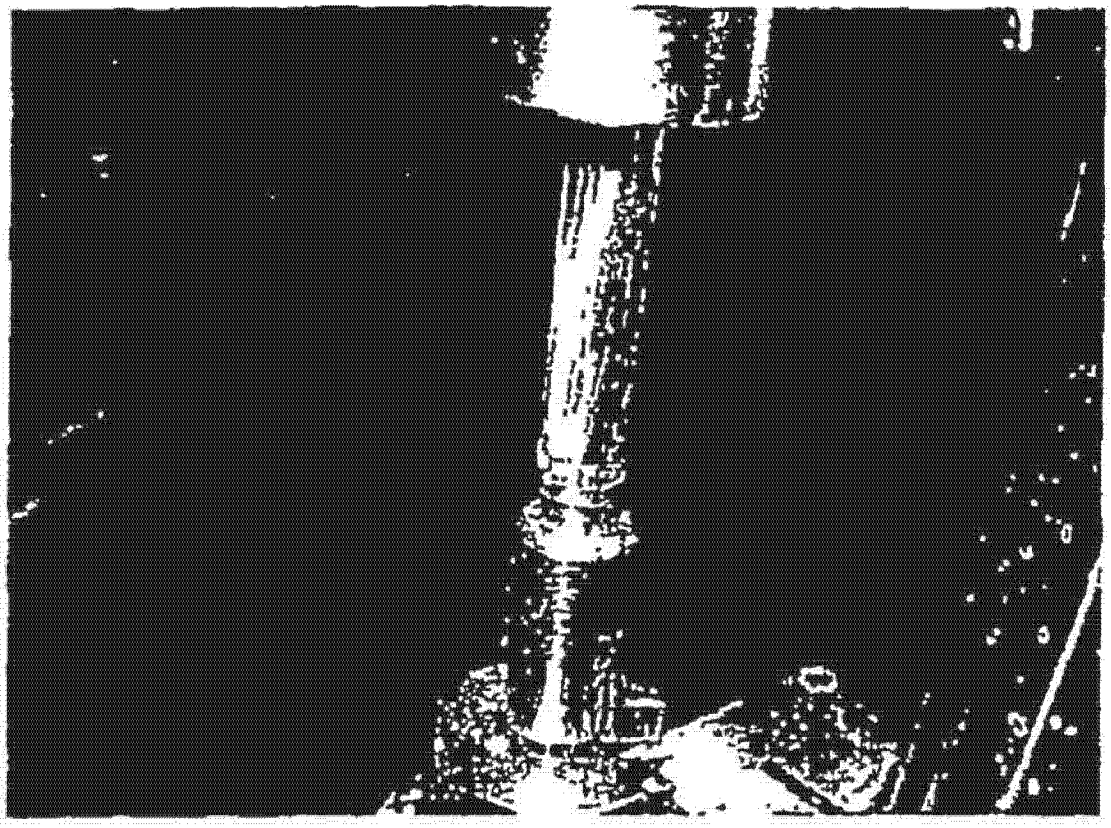
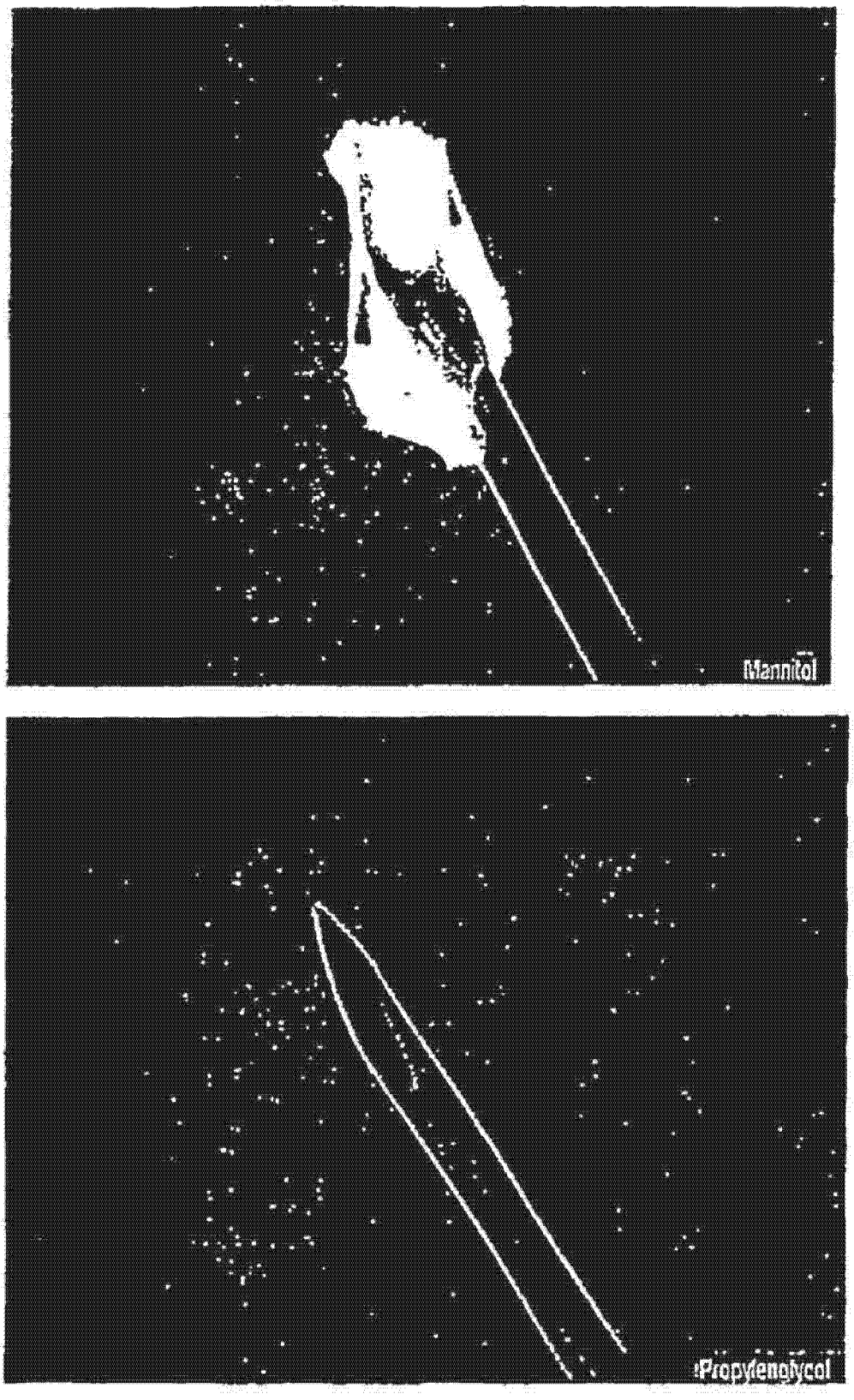


FIGURE 7



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

CROSS REFERENCE TO RELATED APPLICATIONS

This Application is a continuation of International Application serial no. PCT/DK2004/000792 filed Nov. 18, 2004 and claims priority from U.S. application Ser. No. 60/524,653 filed Nov. 24, 2003 and from Danish Application serial no. PA 2003 01719 filed Nov. 20, 2003.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

c) mixing the first and second solutions; and

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

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

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

b) adding propylene glycol to the first solution;

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

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

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

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

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE FIGURES

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

FIG. **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.

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

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

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

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

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

DESCRIPTION OF THE INVENTION

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

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

The formulations of the present invention may be formulated with any peptide where examples of such peptides include, but are not limited to, glucagon, human growth hormone (hGH), insulin, aprotinin, FactorVII, tissue plasminogen activator (TPA), FactorVIIa, FFR-FactorVIIa, heparinase, ACTH, Heparin Binding Protein, corticotropin-releasing factor, angio-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 inhibitors, cytokines, cytokine receptors, PDGF, tumor necrosis factors, tumor necrosis factors receptors, growth factors and analogues as well as derivatives thereof where each of these peptides constitutes an alternative embodiment of the present invention.

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

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

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

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

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

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

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

carbon atoms, even more preferably 8-25 carbon atoms, even more preferably 12-25 carbon atoms, and most preferably 14-18 carbon atoms.

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

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

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

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

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

(a) the amino group attached to the alpha-carbon of the N-terminal amino acid,
(b) the carboxy group attached to the alpha-carbon of the C-terminal amino acid,
(c) the epsilon-amino group of any Lys residue,
(d) the carboxy group of the R group of any Asp and Glu residue,
(e) the hydroxy group of the R group of any Tyr, Ser and Thr residue,
(f) the amino group of the R group of any Trp, Asn, Gln, Arg, and His residue, or
(g) the thiol group of the R group of any Cys residue.

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

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

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

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

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

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

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

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_pNH$—$CO(CH_2)_qCO$—, 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 $CH_3(CH_2)_rCO$—$NHCH(COOH)(CH_2)_2CO$—, 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 —$NHCH(COOH)(CH_2)_4NH$—$CO(CH_2)_uCH_3$, wherein u is an integer from 8 to 18.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_vCO$—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 —$NHCH(COOH)(CH_2)_4NH$—$COCH((CH_2)_2COOH)NH$—$CO(CH_2)_wCH_3$, wherein w is an integer from 10 to 16.

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

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

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

$Val^{8}His^{22}$-GLP-1(7-36)-amide, $Val^{8}His^{22}$-GLP-1(7-37), analogues thereof and derivatives of any of these.

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

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

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

Examples of exendins as well as analogues, derivatives, and fragments thereof to be included within the present invention are those disclosed in WO 97/46584, U.S. Pat. No. 5,424,286 and WO 01/04156. U.S. Pat. No. 5,424,286 describes a method for stimulating insulin release with an exendin polypeptide. The exendin polypeptides disclosed include HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGX;
wherein X=P or Y, and HX1X2GTFITSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS; wherein X1X2=SD (exendin-3) or GE (exendin-4)). WO 97/46584 describes truncated versions of exendin peptide(s). The disclosed peptides increase secretion and biosynthesis of insulin, but reduce those of glucagon. WO 01/04156 describes exendin-4 analogues and derivatives as well as the preparation of these molecules. Exendin-4 analogues stabilized by fusion to serum albumin or Fc portion of an Ig are disclosed in WO 02/46227.

In one embodiment, the exendin-4 analogue is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSS-GAPPSKKKKKK-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 L F Smith; *Nature*, (1960) 4736:483-485, which is hereby incorporated by reference], human insulin analogs, human insulin derivatives or mixtures thereof, where examples of insulin analogs and derivatives are those disclosed in EP 0 792 290 (Novo Nordisk A/S), EP 0 214 826 and EP 0 705 275 (Novo Nordisk A/S), U.S. Pat. No. 5,504,188 (Eli Lilly), EP 0 368 187 (Aventis), U.S. Pat. Nos. 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 β29 (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 (SEMILENTE®) with extended insulin zinc (ULTRALENTE®), sold commercially as LENTE®, insulin glargine (LANTUS®) or extended insulin zinc (ULTRALENTE®), Lys^{B28} Pro^{B29} human insulin (HUMALOG®), Asp^{B28} human insulin, insulin aspart (NOVOLOG®), or a 30/70 mixture of insulin aspart and insulin aspart protamine (NOVOMIX®).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In a further embodiment of the invention the chelating agent is present in a concentration from 0.1 mg/ml to 5 mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 0.1 mg/ml to 2 mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 2 mg/ml to 5 mg/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 stabilizer 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 stabilizer 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 0.1 mg/ml to 50 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1 mg/ml to 5 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 5 mg/ml to 10 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0 mg/ml to 20 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 20 mg/ml to 30 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 30 mg/ml to 50 mg/ml.

In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1 mg/ml to 50 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1 mg/ml to 5 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 5 mg/ml to 10 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 10 mg/ml to 20 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 20 mg/ml to 30 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 30 mg/ml to 50 mg/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), glycerolglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, docusate calcium, docusate potassium, SDS (sodium dodecyl sulfate or sodium lauryl sulfate), dipalmitoyl phosphatidic acid, sodium caprylate, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (e.g. 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, zwitterionic surfactants (e.g. N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (e.g. cetyl-trimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl β-D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35), fusidic acid derivatives—(e.g. sodium tauro-dihydrofusidate etc.), long-chain fatty acids and salts thereof C6-C12 (e.g. oleic acid and caprylic acid), acylcarnitines and derivatives, N^{α}-acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N^{α}-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N^{α}-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof. Each one of these specific surfactants constitutes an alternative embodiment of the invention.

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

The formulations of the invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995, where

such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product.

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

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

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

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

c) mixing the first and second solutions; and

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

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

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

b) adding propylene glycol to the first solution;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLES

Example 1

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

Preparation of Formulations with Different Isotonic Agents

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

TABLE 1

Composition of the tested formulations

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

Osmolarity

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

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

TABLE 2

The measured osmolarity of the formulations

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

Drop Test

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

A photograph of the dried droplets of some of the formulations is shown in FIG. 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}, $Lys^{26}(N^{\epsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

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

Clogging Test

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

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

TABLE 3

Clogging test in NovoPen 1.5 using 30G NovoFine

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

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

Simulated Filling

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

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

Conclusion

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

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

a. propylene glycol was observed to have no influence on the physical and chemical stability of Arg^{34}, $Lys^{26}(N^{\epsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations;
b. propylene glycol was observed to have no influence on antimicrobial preservative testing; and
c. use of propylene glycol would no require that further toxicity studies be tested

Example 2

Comparison of Mannitol and Propylene Glycol-Containing Placebo Formulations in Simulated Filling Studies and Simulated Use Studies

Preparation of Formulations

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

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

Simulated Filling Study

A simulated filling study lasting 24 hours was performed as described in Example 1 and after 24 hours, the filling equipment was inspected for the presence of deposits. No deposits were observed on the filling equipment for the propylene glycol formulation. By comparison, after 24 hours, a lot of deposits were observed on the filling equipment for the mannitol formulation (see FIG. **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. FIG. **7** shows photographs of needles dosed with the propylene glycol (top panel) or mannitol (bottom panel) containing formulations. Deposits on the needle were observed in 48% of the cases when mannitol was used as an isotonic agent whereas no deposits were observed when propylene glycol was used as the isotonic agent.

Example 3

Comparison of Propylene Glycol to Mannitol in Arg^{34}, Lys^{26} (N^{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 and pH was adjusted to the desired pH. Arg^{34}, Lys^{26}(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:

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

Simulated in Use Study

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

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

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

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

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

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

Example 4

Influence of Peptide Concentration on Clogging of Needles

Arg^{34}, Lys^{26}(N^{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 Arg^{34}, Lys^{26}(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.

Example 5

Clogging of Needles in Lys β29 (Nε-tetradecanoyl) des(B30) Human Insulin and NovoMix 30 Formulations Containing Mannitol

Preparation Of Formulations

The Lys β29 (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 β29 (Nε-tetradecanoyl) des(B30) human insulin and zinc acetate dissolved in water

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

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

The composition of Lys β29 (Nε-tetradecanoyl) des(B30) human insulin-containing formulation prepared in the above manner was as follows:

Lys β29 (Nε-tetradecanoyl) des(B30) human insulin (2400 nmol), Phenol (1.80 mg/ml), m-cresol (2.06 mg/ml), Mannitol (30.0 mg/ml), disodiumphosphate, dihydrate (0.890 mg/ml), Sodium chloride (1.17 mg/ml), Zinc acetate (65.4 ug/ml), water for injection (up to 1.0 ml), pH: 7.4

The NOVOMIX® 30-containing formulation was prepared as follows:

a) Prepared a solution by dissolving buffer, sodium chloride, phenol, mannitol and sodium hydroxide in water
b) Prepared a solution of sodium chloride, phenol and mannitol in water
c) Prepared a solution of protamine sulphate in water
d) Prepared a solution of insulin, hydrochloric acid and zinc in water
e) Solutions b), c) and d) were mixed
f) Solution e) was added to the solution of step a)
g) 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:

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 β29 (Nε-tetradecanoyl) des (B30) human insulin on day 2 (5%), day 3 (70%) and on day 4 (100%). Clogging of needles for NovoMix 30 was observed on day 3 (5%), day 4 (10%), day 5 (35%), day 6 (40%), day 8 (50%), day 9 (55%) and day 10 (80%). Thus, the effect of mannitol on the clogging of needles is independent of the type of peptide included in the formulations since a comparable clogging effect was observed with Arg^{34}, Lys^{26}(N^{ε}-(γ-Glu (N^{α}-hexadecanoyl)))-GLP-1(7-37), Lys β29 (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

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 β29 (Nε-tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 mannitol-containing formulations was similar to that observed with Arg^{34}, Lys^{26}(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 β29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30-containing formulations will be similar to that observed with Arg^{34}, Lys^{26}(N^{ε}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations.

SEQUENCE LISTING

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            20                  25                  30

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

The invention claimed is:

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

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

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

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

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

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

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

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

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

10. 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.

11. The formulation according to claim 10, 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.

12. The formulation according to claim 11, wherein said lipophilic substituent has from 8 to 40 carbon atoms.

13. The formulation according to claim 12, wherein said spacer is an amino acid.

14. The formulation according to claim 13, wherein said GLP-1 agonist is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

15. The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of Gly^{8}-GLP-1(7-36)-amide, Gly^{8}-GLP-1(7-37), Val^{8}-GLP-1(7-36) amide, Val^{8}-GLP-1(7-37), $Val^{8}Asp^{22}$-GLP-1(7-36)-amide, $Val^{8}Asp^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}$-GLP-1(7-36) -amide, $Val^{8}Glu^{22}$-GLP-1(7-37), $Val^{8}Lys^{22}$-GLP-1(7-36)-amide, $Val^{8}Lys^{22}$-GLP-1(7-37), $Val^{8}Arg^{22}$-GLP-1(7-36)-amide, $Val^{8}Arg^{22}$-GLP-1(7-37), $Val^{8}His^{22}$-GLP-1(7-36)-amide, $Val^{8}His^{22}$-GLP-1(7-37), Arg^{34}GLP-1(7-37), $Arg^{26,34}Lys^{36}$GLP-1(7-36), Arg^{26}GLP-1(7-37), and Gly^{8}, $Arg^{26,34}Glu^{37}Lys^{38}$GLP-1(7-38) and derivatives of any of these.

16. A method of preparing a GLP-1 agonist formulation suitable for use in an injection device, said method comprising preparing a formulation containing a GLP-1 agonist, propylene glycol, a disodium phosphate dihydrate buffer, and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from about 7.0 to about 10.0, and wherein said GLP-1 agonist, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

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

b) preparing a second solution by dissolving the GLP-1 agonist 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.

17. The method according to claim 16, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

18. The method according to claim 16, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

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

20. The method according to claim 16, wherein the pH of said formulation is about 7.0 to about 9.5.

21. The method according to claim 16, wherein the pH of said formulation is about 7.0 to about 8.0.

22. The method according to claim 16, wherein the pH of said formulation is about 7.2 to about 8.0.

23. A method for reducing deposits on production equipment during production of a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

24. The method according to claim 23, 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.

25. The method according to claim 23, 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.

26. A method for reducing deposits in the final product during production of a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

27. The method according to claim 26, 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.

28. The method according to claim 26, 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.

29. A method for reducing the clogging of injection devices by a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

30. The method according to claim 29, 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.

31. The method according to claim 29, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

* * * * *

Exhibit B

US009265893B2

(12) **United States Patent**
Hansen et al.

(10) **Patent No.: US 9,265,893 B2**
(45) **Date of Patent: Feb. 23, 2016**

(54) **INJECTION BUTTON**

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(73) Assignee: **Novo Nordisk A/S**, Bagsvaerd (DK)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1707 days.

(21) Appl. No.: **12/525,976**

(22) PCT Filed: **Jan. 21, 2008**

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§ 371 (c)(1),
(2), (4) Date: **Dec. 16, 2009**

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PCT Pub. Date: **Aug. 14, 2008**

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(30) **Foreign Application Priority Data**

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A61M 5/00 (2006.01)
A61M 5/315 (2006.01)

(52) **U.S. Cl.**
CPC ***A61M 5/31585*** (2013.01); ***A61M 5/31511*** (2013.01); *A61M 5/3158* (2013.01)

(58) **Field of Classification Search**
CPC A61M 2005/2013; A61M 5/31541; A61M 5/20; A61M 5/31583; A61M 5/3158
USPC 604/181, 187, 218–231
See application file for complete search history.

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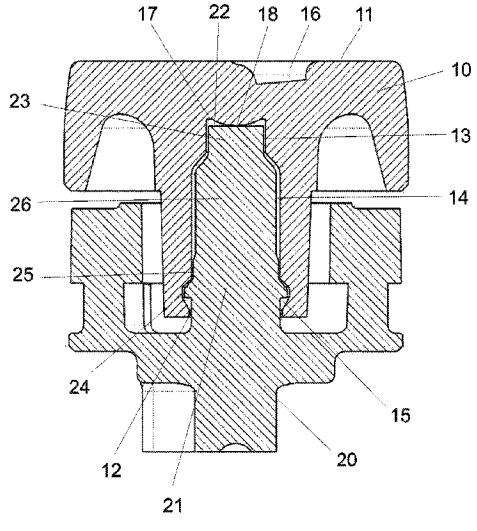
Primary Examiner — Phillip Gray
(74) *Attorney, Agent, or Firm* — Wesley Nicolas

(57) **ABSTRACT**

A push button connection for an injection device comprising a push button (**10**) and a driving part (**20**). The two parts of the push button connection are mounted to each other and is relatively rotatable to each other. In order to minimize the friction occurring between the push button and the driving part when relatively rotated forces are transmitted via a pivot bearing (**18**, **22**). In order also to minimize the effect of forces appearing dislocated from the center line a number of radial bearings (**13**, **23**; **14**, **25**) having a little friction diameter is provided.

6 Claims, 2 Drawing Sheets



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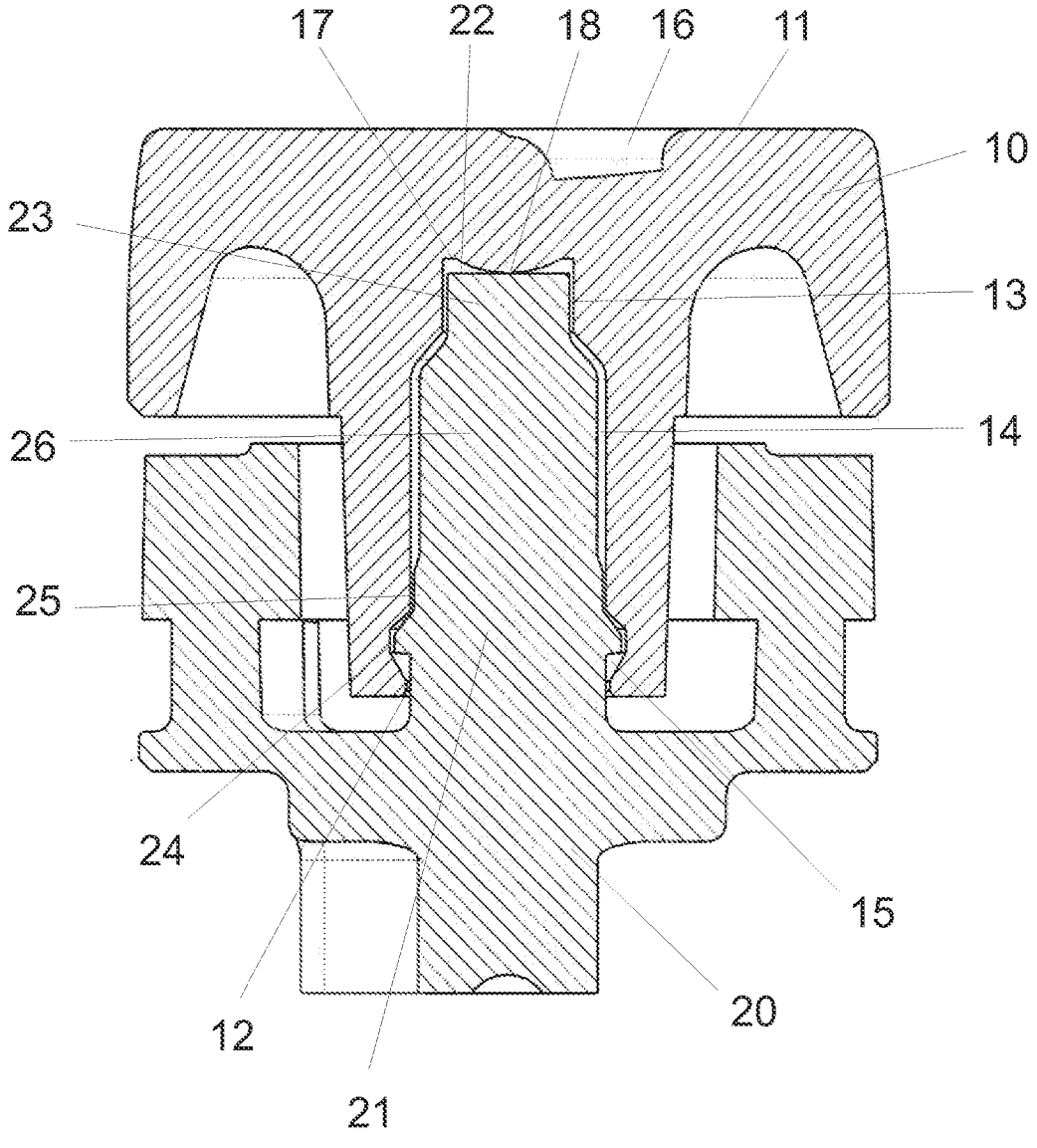

Fig. 1

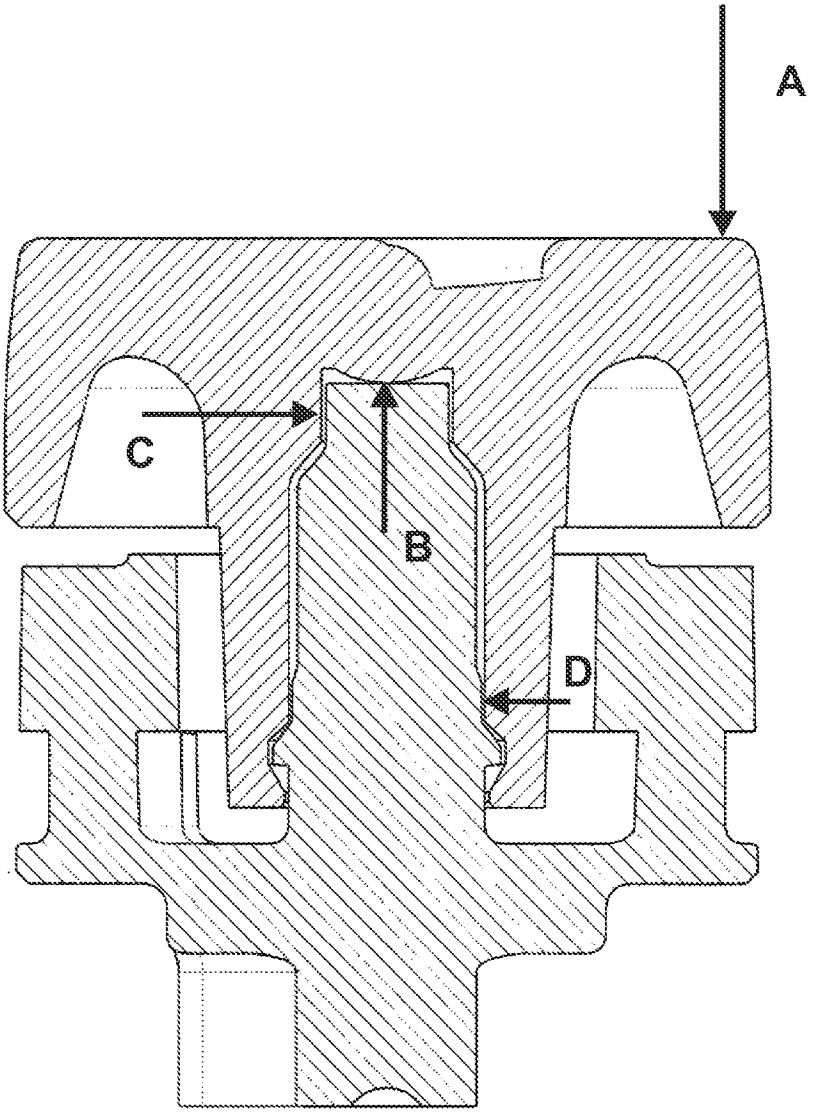

Fig. 2

INJECTION BUTTON

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a 35 U.S.C. §371 national stage application of International Patent Application PCT/EP2008/050624 (published as WO2008/095762), filed Jan. 21, 2008, which claimed priority of European Patent Application 07101729.7, filed Feb. 5, 2007; this application further claims priority under 35 U.S.C. §119 of U.S. Provisional Application 60/899,977, filed Feb. 7, 2007.

THE TECHNICAL FIELD OF THE INVENTION

The invention relates to a push button connection for an injection device and especially to such connection where a push button is rotated relatively to a driving member to which it is connected.

DESCRIPTION OF RELATED ART

U.S. Pat. No. 6,235,004 discloses an injection device in which according to FIG. 15-16 a dose is set by rotating the scale drum out of the housing in a threaded connection. When injecting the set dose the user pushes on the push button which forces the scale drum and the bushing to rotate together back into the housing. During this rotation of the bushing to which the push button is attached, the push button and the bushing rotates relatively to each other. The friction occurring between these relatively rotatable parts contributes to the force a user needs to apply in order to push back the bushing and the scale drum in order to inject the set dose.

U.S. Pat. No. 7,427,275 discloses an injection device in which the push button is formed with a bore encompassing a stem on a sleeve member. The push button and the stem are welded together such that the push button and the sleeve member are axially and rotatably fixed to each other.

DESCRIPTION OF THE INVENTION

It is an object of the present invention to provide a dose button connection for an injection device which minimizes the forces a user must apply to inject a dose.

When a user pushes on the injection button, the force applied is directed to the forward movement of the driving part, however, since the push button and the driving part rotate relatively to each other a friction between these rotating parts will occur. The user therefore also has to apply a force large enough to overcome this friction. One way of minimizing the force a user must apply in order to perform an injection is therefore to minimize this friction. By forming a pivot bearing between the two parts, the surface area of interaction between the two objects can be minimized and the radius of the resulting friction force can be kept at a minimum.

In order to secure the fit between the push button and the driving part and on the same time direct forces applied on the periphery of the push button to the driving part at least one radial bearing between the push button and the protrusion is formed.

Preferably one radial bearing is formed in the upper area and one is formed in the lower area both having the least possible radius of friction. In this way forces applied at in the periphery area of the push button and causing tilting of the push button on the protrusion of the driving part is properly transferred.

If a user applies a force eccentric to the centre axis of the push button i.e. on a peripheral area of the button, the push button will tilt and a reaction torque will occur at the radial bearings. In order to minimize this force pair, which in this load case is located at the distance from the radial bearing surface to the centre axis of the system, this distance, which again equals the radius of the protrusion, must be as little as possible and the distance between the bearings as long as possible. However, in order not to make the protrusion too narrow and fragile it is preferred to balance the radius of the bearings, such that the upper bearing has the smallest diameter and the lower bearing at the root of the column shaped protrusion has a diameter large enough to resist the bending force as a result of the offset applied push button forces.

In order to assemble the push button in an irreversible manner making it difficult to dissemble, it is preferred to secure the push button at the intended position by adding a track into which a rim on the harder part is forced during the manufacture of the injection device. The necessary compliance of the push button for the assembly snap-on can be secured by selection of a soft material and/or a vertical slit in the hollow section of the geometry.

Further the materials used for the push button and the protrusion on the driving part could be materials having low internal friction, or the materials could be surface treated in order to lower the internal friction.

The push button used in the connection has a central bore dedicated to engage the protrusion provided on the driving part. The bottom of the bore is preferable formed with a pivot. This pivot bears on a surface of the protrusion thus forming a pivot bearing.

DEFINITIONS

An "injection pen" is typically an injection apparatus having an oblong or elongated shape somewhat like a pen for writing. Although such pens usually have a tubular cross-section, they could easily have a different cross-section such as triangular, rectangular or square or any variation around these geometries.

As used herein, the term "drug" is meant to encompass any drug-containing flowable medicine capable of being passed through a delivery means such as a hollow needle in a controlled manner, such as a liquid, solution, gel or fine suspension. Representative drugs includes pharmaceuticals such as peptides, proteins (e.g. insulin, insulin analogues and C-peptide), and hormones, biologically derived or active agents, hormonal and gene based agents, nutritional formulas and other substances in both solid (dispensed) or liquid form.

All references, including publications, patent applications, and patents, cited herein are incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

All headings and sub-headings are used herein for convenience only and should not be constructed as limiting the invention in any way.

The use of any and all examples, or exemplary language (e.g. such as) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention. The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability, and/or enforceability of such patent documents.

This invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be explained more fully below in connection with a preferred embodiment and with reference to the drawings in which:

FIG. **1** Show a cross section view of the connection between a push button and a driving part.

FIG. **2** Show a cross section view of the connection and the forces occurring.

The figures are schematic and simplified for clarity, and they just show details, which are essential to the understanding of the invention, while other details are left out. Throughout, the same reference numerals are used for identical or corresponding parts.

DETAILED DESCRIPTION OF EMBODIMENT

When in the following terms as "upper" and "lower", "right" and "left", "horizontal" and "vertical", "clockwise" and "counter clockwise" or similar relative expressions are used, these only refer to the appended figures and not to an actual situation of use. The shown figures are schematic representations for which reason the configuration of the different structures as well as there relative dimensions are intended to serve illustrative purposes only.

In that context it may be convenient to define that the term "distal end" in the appended figures is meant to refer to the end of the injection device carrying the injection needle whereas the term "proximal end" is meant to refer to the opposite end pointing away from the injection needle.

FIG. **1** discloses the connection between the push button **10** and the driving part **20**.

When a user wants to inject a dose, which he or she has first selected, the user pushes the push button **10** which then moves the driving part **20** axially forward in the injection device. During this forward movement of the driving part **20** it also rotates usually because it is interfaced with a dose dial drum which is threadedly connected to a housing. Such injection device is described in details in EP 1.003.581. The combined axial and rotatable movement of the driving part **20** drives the set dose out from the injection device.

As the users finger pushes on the push surface **11** of the push button **10** it is unable to rotate due to the friction between the users finger and the push button **10** whereas the driving part **20** is forced to rotate due to its interface, therefore a relative rotation between the push button **10** and the driving part **20** takes place.

The push button **10** which could be manufactured from a suitable polymeric material being softer that the material from which the driving part **20** is manufactured comprises at the proximal end a push surface **11** which is contacted by the user's finger when a dose is to be injected and an opposite located cylindrical bore **12** with a circular cross section. The most proximal part **13** of the bore **12** has a smaller diameter than the remaining part **14** of the bore **12**. At the distal end of the bore **12**, a radial extending track **15** is provided.

The push surface **11** could be provided with a tactile cut-out **16** informing visual impaired users on the content of the injection device and the most proximal bottom surface **17** of the bore **12** is formed with a raised pointer forming a pivot **18**.

The driving part **20** is provided with a protrusion **21** having a circular cross section and a top surface **22**. This protrusion **21** has at its proximal end a top part **23** with a decreased diameter compared to the remaining part **26** of the protrusion **21**. Further the protrusion **21** is provided with a radial extending rim **24** at its distal end. In the area around this rim **24**, the protrusion **21** is provided with a belt **25** with a slightly raised diameter.

When the push button **10** is mounted on the protrusion **21** of the driving element **20** it is simply clicked on such that the extending rim **24** enters the track **15**. This forms a connection almost impossible to disconnect since the polymeric material of the push button **10** is softer than the material from which the protrusion **21** is produced. In this position the pivot **18** formed in the most proximal bottom surface **17** of the bore **12** bears on the top surface **22** of the protrusion **21** thus forming a pivot bearing **22**, **18**. Further the push button **10** is radially supported by the protrusion **21** at the top part **23** forming a radial top bearing **23**, **13**. The belt **25** on the protrusion **21** bears on an area of the remaining part **14** of the bore **12** thus forming a radial bottom bearing **14**, **25**.

In FIG. **2** the push button **10** connection is disclosed with the various forces occurring when a user applies an injection force in the peripheral area of the push button **10**.

When the user applies an injection force A at the peripheral area of the push button **10** a vertical reaction force B will appear at the pivot point **22**, **18**, at the same time a radial force C will occur at the upper radial bearing **13**, **23**. Since the upper radial bearing **13**, **23** are located at the top part **23** having the smaller diameter, the resulting torque is relatively small. Further, a radial force D will occur at the lower radial bearing **14**, **25**, however due to the distance between the upper radial bearing **13**, **23** and the lower radial bearing **14**, **25**, the force resulting on the lower radial bearing **14**, **25** is relatively small.

Some preferred embodiments have been shown in the foregoing, but it should be stressed that the invention is not limited to these, but may be embodied in other ways within the subject matter defined in the following claims.

The invention claimed is:

1. A push button connection for an injection device comprising:

a push button mountable on a driving part being rotatable relatively to the push button and which push button further comprises a bore with a bottom surface and which bore surrounds a protrusion on the driving part which protrusion has a top surface and wherein a pivot bearing is formed between the bottom surface and the top surface, wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button.

2. A push button connection according to claim **1**, in which at least one radial bearing between the push button and the driving part is provided.

3. A push button connection according to claim **2**, in which an upper radial bearing is provided at a top part of the protrusion and a lower radial bearing is provided at the bottom of the protrusion.

4. A push button connection according to claim **3**, in which the top part of the protrusion accommodating the upper radial bearing has a diameter smaller than the diameter of the remaining part of the protrusion.

5. A push button connection according to claim **1**, in which the push button is manufactured from a polymeric material being softer than the material from which the driving part is manufactured.

6. A push button connection according to claim 1, in which the protrusion is provided with an extending rim mating with a track provided in the push button.

* * * * *

Exhibit C

US00RE41956E

(19) **United States**

(12) **Reissued Patent**

Klitgaard et al.

(10) **Patent Number: US RE41,956 E**

(45) **Date of Reissued Patent: *Nov. 23, 2010**

(54) **DOSE SETTING LIMITER**

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(*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/122,211**

(22) Filed: **May 4, 2005**

Related U.S. Patent Documents

Reissue of:

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Appl. No.: **09/655,922**
Filed: **Sep. 6, 2000**

U.S. Applications:

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A61M 5/178 (2006.01)
A61M 5/315 (2006.01)

(52) **U.S. Cl.** **604/181**; 604/186; 604/207; 604/208; 604/211; 604/224

(58) **Field of Classification Search** 604/181, 604/186, 187, 207–208, 211, 224
See application file for complete search history.

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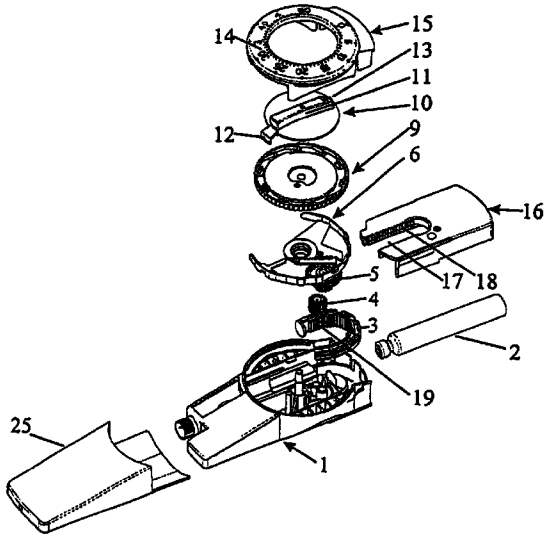
(57) **ABSTRACT**

A limiting mechanism which prevents the setting of a dose, which exceeds the amount of liquid left in a cartridge of an injection device, is disclosed. The injection device is the type where a dose is set by rotating a dose setting member relative to a driver and away from a fixed stop in the injection device. The dose setting member interfaces the driver such that the dose setting member can be rotated in one direction without rotating the driver. The dose is injected by rotating back the dose setting member which during the backward rotation carries the driver with it. Rotating the driver causes the piston rod to move forward inside the cartridge and expel some of the liquid contained in the cartridge. The driver is provided with a track having a length which is related to the total amount of liquid in the cartridge and which track is engaged by a track follower coupled to the dose setting member to follow rotation of this dose setting member. Each time a dose is set and injected, the track follower moves further into the track. When the track follower reaches the end of the track the dose setting member can not be rotated further, and a dose larger than the remaining liquid in the cartridge cannot be set.

19 Claims, 2 Drawing Sheets



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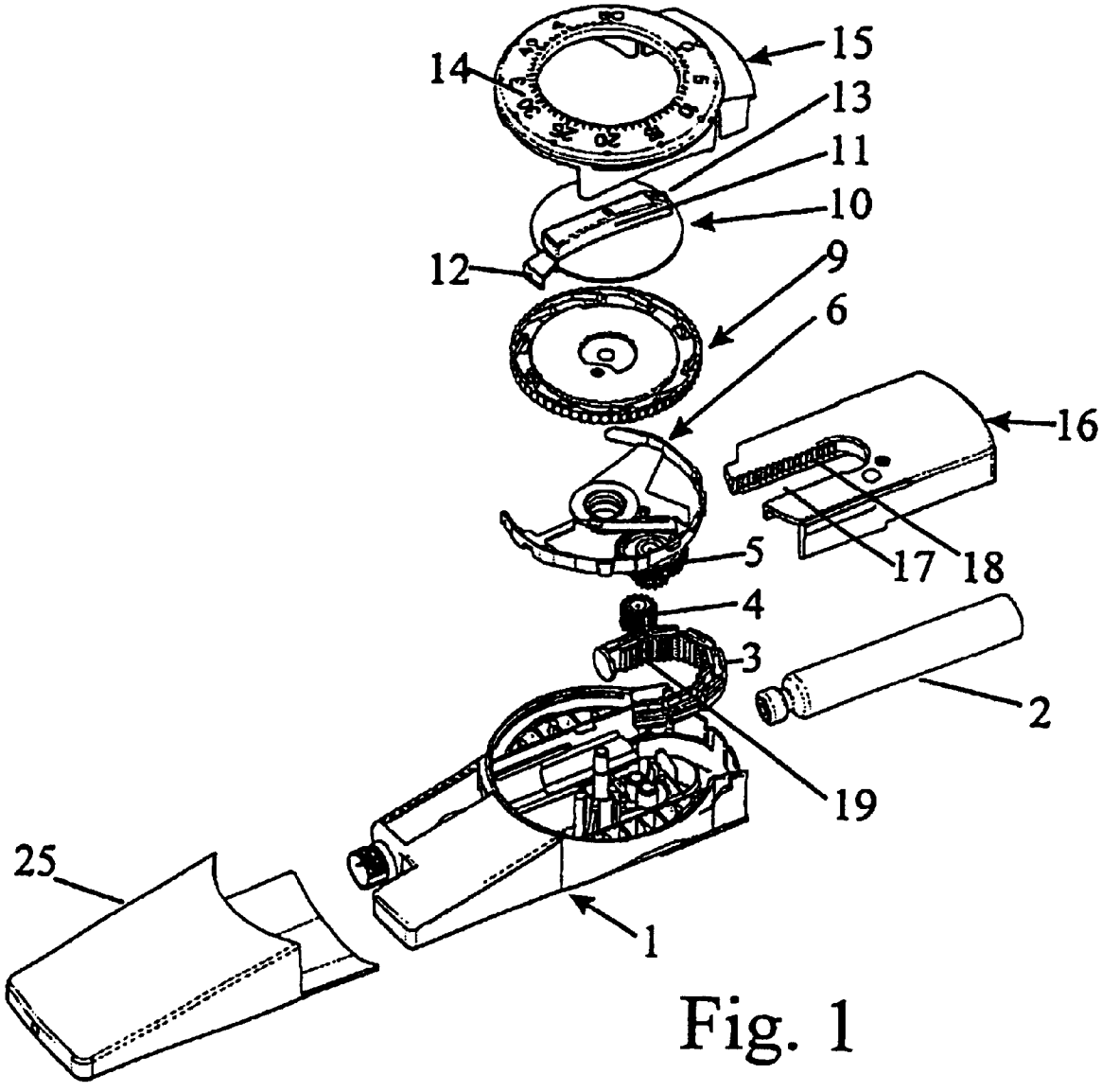


Fig. 1

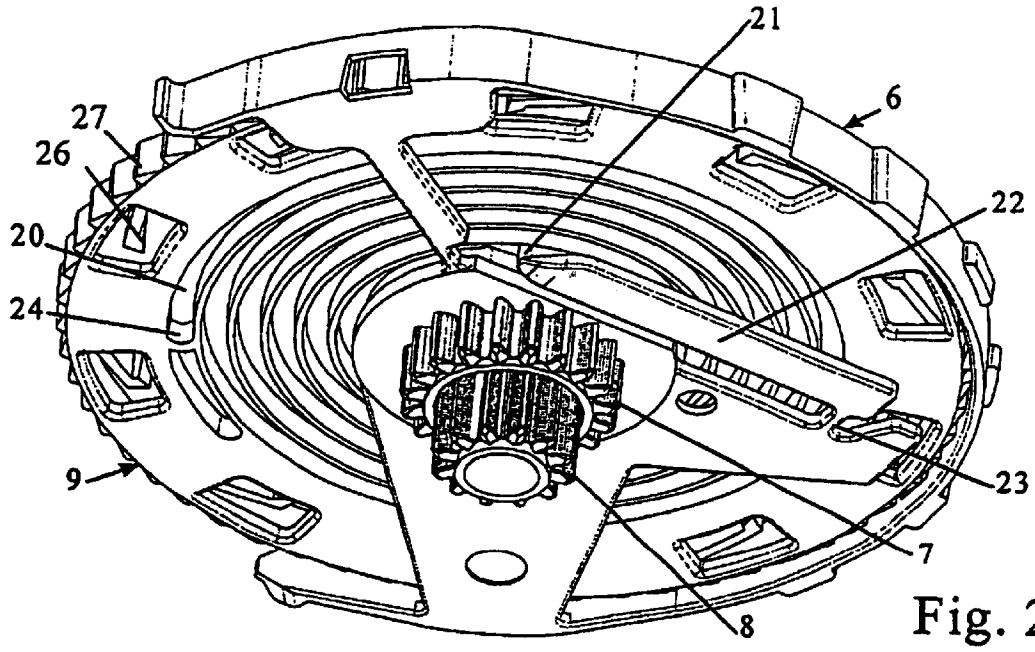


Fig. 2

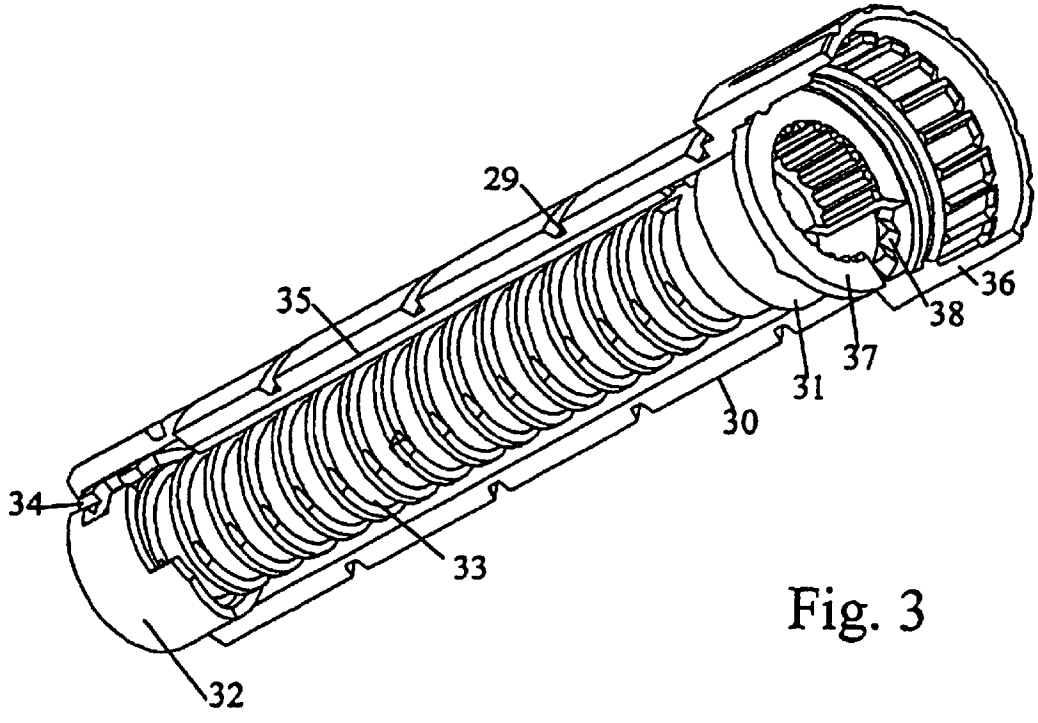


Fig. 3

DOSE SETTING LIMITER

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application *is a reissue of U.S. Pat. No 6,582,404, which* claims priority under 35 U.S.C. 119 of U.S. provisional application No. 60/155,612 filed on Sep. 23, 1999 and Danish application no. PA 1999 01309 filed on Sep. 16, 1999, the contents of which are fully incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to injection devices wherein the contents of a cartridge are injected as a number of individually set doses.

Such devices have a dose setting mechanism by which the doses are set for subsequent injecting when an injection button is operated. This can be obtained by moving a carrier along a piston rod a distance proportional to the wanted dose and subsequently moving the carrier back to its original position so that the carrier carries the piston rod with it instead of being moved along said piston rod.

SCOPE OF THE RELATED ART

From EP 327 910 is known a syringe by which a dose is set by screwing a nut member up along a threaded piston rod away from a stop in a housing. The set dose is injected by pressing the end of the nut member that forms an injection button whereby the nut member is moved back to abutment with the stop again. During the latter movement of the nut member the piston rod is carried along by the nut that does not move relative to this piston rod during the injection.

When a dose is set it is convenient if a limiting device is provided which makes it impossible to set a dose that exceeds the amount of medicament which is left in the cartridge. In EP 327 910 this is obtained by the fact that the thread of the piston rod has such a length that the cartridge is just emptied when the nut is screwed to the end of the thread and then pressed home to its abutment with the stop. By setting a dose the nut can only be screwed to the end of the thread and thereby the size of the last dose is limited to comprise the remaining amount in the cartridge.

The distance the injection button has to be moved corresponds to the distance the piston in the cartridge has to be moved to inject the set dose. Especially by larger cartridges with a large cross section diameter this distance can be very short. To obtain a larger movement of the injection button a sort of gearing may be used so that the distance the injection button has to be moved is proportional with the injected dose but is a number of times the movement of the piston in the cartridge.

EP 608 343 describes an example of such a geared dose setting and injection mechanism. In this device the carrier does not cooperate directly with the threaded piston rod but with a driver element which can move the piston rod when a set dose is injected. In this device the driver element comprises a nut member which is fixed against axial displacement in the injection device. The thread of the nut member engages an outer thread of the piston rod which is secured against rotation in the injection device. By the setting of a dose the carrier is rotated away from a stop to which it is returned when the injection button is operated. During its return the carrier rotates the driver element that moves the piston rod further into the cartridge to press the piston of this cartridge so that a set amount of the medicament in the cartridge is pressed out through an injection needle at the distal end of the cartridge. As the nut member is not moved relative to the piston rod during the setting of a dose, a limiting construction as described above cannot be provided limiting the dose so it does not exceed the amount of liquid left in the injection device.

OBJECT AND SUMMARY OF THE INVENTION

An object of the invention is to provide a limiting mechanism which prevents setting of a dose that exceeds the amount of liquid left in a cartridge of an injection device of the geared type wherein a dose is set by rotating a dose setting member relative to a driver and away from a fixed stop in the injection device, and the dose is injected by rotating back the dose setting member which during this rotation carries the driver element with it to rotate this driver element which moves the piston rod forward.

Such a mechanism is according to the invention characterized in that the driver element is provided with a track having a length which is related to the total amount of medicament in the cartridge and which track is engaged by a track follower coupled to the dose setting member to follow rotation of said dose setting member. During the setting of a dose the track follower will be advanced in the track of the driver to a position depending on the set dose as during dose setting the dose setting member and the driver are rotated relative to each other. As during the injection the driver follows the rotation of the dose setting member, the pin of the dose setting member will keep its position in the track of the driver when the set dose is injected. The length of the track is so adapted that the pin reaches the end of the track and makes an increase of the set dose impossible when a dose is set which corresponds to the amount of liquid remaining in the cartridge.

According to the invention the driver may be disk shaped and have a spiral shaped track which is engaged by a cam on a member which is flexibly coupled to the dose setting member so that the pin can be moved radially when it follows the track of the driver.

In another embodiment of the invention the driver may be cylindrical and have a helical track which is engaged by a cam on the dose setting member which is a cylinder concentric with the driver.

The track may be provided as a thread in the driver and the track follower may be a nut shaped member coupled to the dose setting member and provided with a thread engaging the thread of the driver. When a dose is set the dose setting member is screwed with its thread along the thread of the driver. The limitation of the set dose is obtained by giving the threads an appropriate length.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following the invention will be explained in further details with references to the drawing, wherein

FIG. **1** shows an exploded view of a syringe with a dose limiter according to the invention;

FIG. **2** shows an enlarged view of the dose setting element and the driver element of the syringe in FIG. **1**; and

FIG. **3** shows the dose setting member, the driver, and the track follower of another embodiment of an injection syringe.

DETAILED DESCRIPTION OF THE INVENTION

The syringe in FIG. **1** comprises a housing **1** accommodating a cartridge **2** from which the content can be pressed out by a piston rod **3** which is by injection via gear wheels **4** and **5** advanced a distance corresponding to a dose set by dose setting. A dose setting member **6** is provided with a toothed wheel **7** surrounding a central bore through which a pinion **8** on a driver **9** projects as it is shown in FIG. **2**. The dose setting element **6** is operated through an operation element **10** which has a finger grip **11**, a carrier **12** which engages the dose setting member **6**, and a arrow **13** pointing on a scale **14** provided on a lid **15** which forms a part of the housing **1**. FIG. **1** further shows a cap **25** which can be put on to protect a not shown needle which may be mounted on the syringe, and an injection button **16** which is sliding mounted in the housing **1** and which has a recess **17** which is on one of its side surfaces provided with a cogging **18**.

In the assembled syringe the toothed wheel **7** on the dose setting member **6** engages the cogging **18** of the button element **16** whereas the pinion **8** on the driver **9** engages the part with the large diameter of the gear wheel **5** the part of which with the small diameter engages the other gear wheel **4** which further engages a cogging **19** on the piston rod **3**.

The driver member **9** is provided with pawl **26** which with not shown teeth in the housing forms an unidirectional coupling allowing the driver **9** to rotate only in the direction by which the piston rod **3** is advanced into the cartridge **2**. A ratchet is provided by saw tooth shaped protrusions on the dose setting element **6** engaging a saw tooth cogging **27** at the perimeter of the driver **9**, this ratchet being so oriented that only rotation of the dose setting member **6** in the direction in which the driver **9** can move is transmitted from the dose setting member **6** to the driver **9**. By rotation of the dose setting member **6** in the opposite direction the teeth of the ratchet parts will ride over each other.

To set a dose the finger grip **11** of the operation element **10** is gripped and the element **10** is rotated clockwise until the arrow points at the wanted dose on the scale **14**. As mentioned this rotation will make the ratchet parts of the dose setting element and the driver ride over each other. If the dose setting member **6** is rotated in the clockwise direction to reduce the set dose, the ratchet will cause transmission of the rotation from the dose setting member **6** to the driver **9**, but the when a torque in this direction is transmitted from the operating element through the carrier **12** to the dose setting member **6**, this dose setting member is deformed so that the protrusion on the dose setting member **6** is drawn out of its engagement with the toothing **27** of the driver **9** and an anticlockwise rotation of the dose setting member **6** is allowed without the rotation being transmitted to the driver **9**.

Due to the engagement between the toothed wheel **7** on the dose setting member **6** and the cogging **18** of the injection button **16** this button will be lifted from the end of the housing **1** when a dose is set and will be lowered when a dose is reduced.

When the injection button **16** is pressed to inject a set dose the engagement between the toothed wheel **7** on the dose setting member **6** and the cogging **18** of the injection button **16** will cause the dose setting member **6** to rotate in an anticlockwise direction. As the torque is not transmitted to the dose setting member **6** by the operating element **10**, the ratchet coupling between the dose setting member **6** and the driver **9** will be active and the driver **9** will be rotated with the dose setting member **6** in the anticlockwise direction and will drive the piston rod **3** into the cartridge.

As it is seen in FIG. **2** the disk shaped driver **9** has in its side facing the dose setting member **6** a spiral shaped track

20 which is engaged by a cam **21** provided at the end of an arm **22** which is by a flexible beam **23** fastened to the dose setting member **6** so that the arm **22** can swing to let the cam **21** move in the radial direction of the driver **9**. When the dose setting member **6** during the setting of a dose is rotated relative to the driver **9** the cam is moved along the track **20** whereas the cam during the injection due to the concomitant rotation of the dose setting member **6** and the driver **9** remains in its position in the track **20** obtained during the dose setting. This way the position of the cam in the track reflects the total amount of medicine administered. When the cam **21** abuts the end wall **24** of the track **20** the set dose cannot be increased and by adapting the length of the track to the total amount of medicine in the cartridge it is ensured that a dose larger than the amount of medicine remaining in the cartridge cannot be set.

FIG. **3** shows a dose setting member **30** surrounding a driver **31** of another embodiment of a dose setting limiter. The dose setting member **30** is cylindrical and is on its outer wall provided with a helical track **29** which is designed to co-operate with a helical inner ridge in a not shown housing so that the dose setting member **30** is screwed outward in said housing when rotated to set a dose and inward in said housing when rotated to reduce a too large set dose. During the dose setting rotation the dose setting member **30** is rotated freely relative to the driver **31** which it surrounds. Between the dose setting member **30** and the driver **31** a nut member **32** is coupled which can when it is rotated relative to the driver **31** be screwed up along this driver which is at its outer surface provided with a helical track **33**. At its outer wall the nut member **32** is in the axial direction provided with a recess **34** which is engaged by a ridge **35** in the axial direction on the inner side of the dose setting element **30**.

During the setting of a dose the nut member **32** is due to the engagement between the ridge **35** and the recess **34** rotated with the dose setting member **30** relative to the driver **31** so that the position of the nut member **32** on this driver is dependent on the dose set. When the dose is injected by pressing a not shown injection button which is placed in an end part **36** of the dose setting member **30** this button presses a flange **37** at an end of the driver **31** into engagement with coupling teeth **38** at the bottom of the end part **36** of the dose setting member **30**. On its lower not visible side the flange **37** is provided with coupling teeth corresponding to the coupling teeth **38** of the dose setting member **30** and when the dose setting member **30** is due to the engagement between the track **29** in the dose setting member **30** and the ridge in the housing forced to rotate relative to the housing when it is pressed into the housing the rotation will be transmitted to the driver **31** which due to the engaging coupling teeth is forced to rotated with the dose setting member and during this rotation the nut member **32** will maintain its position on the driver **31**. This way the position of the nut member **32** on the driver **31** will always indicate the total sum of set and injected doses. When the length of the helical track **33** in the driver **31** is adapted to the amount of medicine in a cartridge the nut member **32** will reach the end of the track **33** and stop for setting a dose larger than the amount remaining in the cartridge.

What is claimed is:

1. A limiting mechanism that prevents setting of a dose that exceeds the *injectable* amount of liquid left in a cartridge of an injection device wherein a dose is set by rotating a dose setting member relative to a driver and away from a fixed stop in the injection device, and the dose is injected by **[**rotating**]** *pressing an injection button which rotates* back the dose setting member which during this rotation carries the

driver with it to rotate this driver which moves the piston rod forward, wherein the driver is provided with a track having a length which is related to the total *injectable* amount of medicament in the cartridge and which track is engaged by a track follower coupled to the dose setting member to follow rotation of this dose setting member and wherein the driver is disk shaped and the track has a spiral shape which is engaged by the track follower which is flexibly coupled to the dose setting member so that the track follower can be moved radially when it follows the track of the driver element.

2. A limiting mechanism that prevents setting of a dose that exceeds the amount of liquid left in a cartridge of an injection device wherein a dose is set by rotating a dose setting member relative to a driver and away from a fixed stop in the injection device, and the dose is injected by rotating back the dose setting member which during this rotation carries the driver with it to rotate this driver which moves the piston rod forward, wherein the driver is provided with a track having a length which is related to the total amount of medicament in the cartridge and which track is engaged by a track follower coupled to the dose setting member to follow rotation of this dose setting member and wherein the driver is cylindrical and the track has a helical shape which is engaged by the track follower which is coupled to the dose setting member so that the track follower can be moved rotationally when it follows the track of the driver element.

3. The limiting mechanism of claim **2**, wherein the dose setting element is a cylinder concentric with the driver.

4. The limiting mechanism of claim **3**, wherein the track comprises a thread in the driver and that the track follower comprises a nut shaped member coupled to the dose setting member and provided with a thread engaging the thread of the driver.

5. A dose setting limiter assembly that prevents the setting of a dose which exceeds the remaining injectable amount of medication in a multiple dose cartridge in an injection device which comprises: a cylindrical dose setting member having an outer wall provided with a helical groove which allows the cylindrical dose setting member to be screwed out of the injection device and away from an initial position when the cylindrical dose setting member is rotated during dose setting and screwed into the device and toward the initial position to reduce the size of a set dose, wherein during injection of the set dose the cylindrical dose setting member is pressed back into the device and as a result of the helical groove it rotates back toward the initial position;

wherein the dose setting limiter assembly comprises:

(a) a helical track disposed on the outer surface of a hollow cylindrical driver that drives a separate piston rod forward; and

(b) a follower that engages the helical track;

wherein the follower moves along the helical track when the dose setting member is rotated during dose setting; but wherein the follower does not move along the track during injection of the set dose; wherein the injection of the set dose is carried out by pressing an injection button which:

(i) presses the cylindrical dose setting member back into the device, and

(ii) causes the cylindrical dose setting member to rotate back to the initial position, wherein the rotation back is cause by the helical groove on the dose setting member;

wherein the position of the follower along the track is indicative of the total sum of the set and injected doses;

wherein the length of the helical track that the follower can move along corresponds to the amount of medication in the cartridge that is available to be injected; and

wherein the follower abuts a stop at the end of the track during dose setting before the cylindrical dose setting element can be rotated to dial up a dose that would exceed the injectable amount of medication remaining in the cartridge.

6. The dose setting limiter assembly of claim 5, wherein when the follower abuts the stop at the end of the track during dialing up of a dose, the cylindrical dose setting member cannot be rotated further to increase the size of the dose.

7. The dose limiter assembly of claim 6, wherein the follower is a nut like element and the helical track is a thread and wherein the follower engages the thread.

8. The dose limiter assembly of claim 7, wherein the driver, the helical grove, the helical track, and the dose setting member are oriented so that they are all coaxial.

9. A dose limiter mechanism for use with in an injection device, which comprises:

(i) a rotatable hollow cylindrical dose setting member containing a threaded groove on its outer surface so that it screws out of the injection device during setting of a dose when it is rotated, screws back into the housing to reduce the size of a set dose when it is rotated back, and screws back into the housing when an injection button is pressed during injection, and

(ii) a hollow cylindrical piston rod driver that is coaxial with the hollow cylindrical dose setting member;

wherein the dose limiting mechanism operates within the injection device to prevent the setting of a dose that exceeds the injectable amount of medication remaining in a multiple dose cartridge in the device; and wherein the dose limiter mechanism comprises:

a helical track disposed on the outer surface of the piston rod driver, the helical track having a length that corresponds to the injectable amount of medication in the cartridge; a follower that engages the helical track and moves along the helical track when the dose setting member is rotated during dose setting but that remains in a fixed position on the helical track when the dose setting member is rotated back when the injection button is pressed during injecting of medication, and wherein the distance the follower moves during dose setting corresponds to the size of the set dose and wherein the follower abuts a stop at the end of the helical track when an attempt is made to rotate the dose setting member during dose setting that would result in a dose being set that exceeds the remaining injectable amount of medication in the cartridge.

10. The mechanism of claim 9, wherein the hollow cylindrical dose setting member is prevented from rotating to increase the size of a set dose when the follower hits the stop.

11. The mechanism of claim 9, wherein the track on the hollow cylindrical piston rod driver forms a thread and follower comprises a nut like element that threadly engages the thread.

12. The mechanism of claim 10, wherein the track on the hollow cylindrical piston rod driver forms a thread and the follower comprises a nut like element that threadly engages the thread.

13. An injection device dose limiter assembly for use with both

(a) a rotatable cylindrical dose setting member, which threadly engages an injection device housing element

so that (i) when it is rotated to set the size of a dose it screws out of an injection device housing, (ii) when it is rotated back to reduce the size of a set dose it screws back into the housing, and (iii) when an injection button is pressed during injecting of medication the cylindrical dose setting member is pressed back into the housing and rotates back, and

(b) a hollow cylindrical piston rod driver that drives a separate piston rod during injection of the set dose;

wherein the injection device dose limiter prevents the setting of a dose that is larger than the injectable amount of medication remaining in a multi dose cartridge and

wherein the injection device dose limiter assembly comprises:

a helical track disposed on the outside of the hollow cylindrical piston rod driver; and

a follower that moves along the track during dose setting but remains stationary with respect to the helical track during dose injecting when an injection button is pressed which causes the cylindrical dose setting member to be screwed back into the housing; wherein the length of the track that the follower is capable of moving along corresponds to the injectable amount of medication in an injection device multiple dose cartridge; and

wherein during dose setting:

the follower moves a distance along the track that corresponds to the size of the dose being set; and

wherein the follower abuts a stop before the size of the set dose exceeds the injectable amount of medication remaining in the cartridge.

14. The assembly of claims 5 or 13, wherein the follower abuts the stop when the size of the set dose equals the injectable amount of medication remaining in the cartridge.

15. The assembly of claims 5 or 13, wherein the helical track has a length adapted to ensure that the follower stops advancing when the size of a set dose is equal to that remaining for injection.

16. The assembly of claims 1, 5, or 13, wherein the injection button moves a distance proportional to, but a number of times greater than, the distance a piston in the cartridge moves during delivery of the set dose during dose injecting.

17. The mechanism of claim 9, wherein the follower abuts the stop when the size of the set dose equals the injectable amount of medication remaining in the cartridge.

18. The mechanism of claim 9, wherein the helical track has a length adapted to ensure that the follower stops advancing when the size of a set dose is equal to that remaining for injection.

19. The mechanism of claim 9, wherein the injection button moves a distance proportional to, but a number of times greater than, the distance a piston in the cartridge moves during delivery of the set dose during dose injecting.

* * * * *

Exhibit D

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the **PATENT APPLICATION** of:	
Hansen et al.	Our File: 7543.204-US
Application No.: 12/525,976	Date: July 25, 2013
Confirmation No.: 2853	
Filed: December 16, 2009	
For: INJECTION BUTTON	
Group: 3767	
Examiner: Gray, Phillip A	

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal is from the Examiner's decision to finally reject claims 1-6 and 8 as set forth in the Final Office Action sent from the U.S. Patent and Trademark Office on November 26, 2012.

A Notice of Appeal was filed March 26, 2013, in response to the Final Office Action of November 26, 2012. An Extension of Time extending the time for filing the Appeal Brief from May 26, 2013 to July 26, 2013 was submitted previously. No additional fees are believed necessary for filing the instant Appeal Brief. However, if for any reason additional fees are required for consideration of the instant paper

or any accompanying document, this paper should be treated as the appropriate request or petition and authorization is hereby given to charge the fees to Deposit Account No. 14-1447.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Novo Nordisk A/S, of Bagsvaerd, Denmark, the assignee of record. The assignment was recorded in the U.S. Patent and Trademark Office on December 16, 2009, at Reel 023664, Frame 0067.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' representative or the Assignee are not aware of any other prior or pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claim 1 is currently pending. Claim 1 stands finally rejected. Thus, finally rejected claim 1 is at issue in the instant appeal and form the subject matter of the instant Appeal Brief. The claim at issue is attached in the "Claims Appendix." The appeal contains 1 independent claim, namely claim 1.

IV. STATUS OF AMENDMENTS

An Amendment under 37 C.F.R. §1.116 was filed on July 22, 2013 pursuant to 37 C.F.R. 41.33(a). The amendment addresses formal issues and does not alter the scope of the claims. Accordingly, the claims presented for appeal are those filed in the Amendment under 37 C.F.R. § 1.116 and 37 C.F.R. § 41.33(a) filed on July 22, 2013.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is directed to a push button connection for an injection device including:

a push button mountable on a driving part being rotatable relatively to the push button (See e.g., page 4, lines 26-29, Figure 1 - reference numbers 10 and 20);

the push button further comprises a bore with a bottom surface (See e.g., page 5, lines 4-7 and 12-13, Figure 1 - reference numbers 12 and 17);

the bore surrounds a protrusion on the driving part (See e.g., page 5, lines 15-16, Figure 1 - reference numbers 12, 20 and 21);

the protrusion has a top surface and wherein a pivot bearing is formed between the bottom surface and the top surface (See e.g., page 5, lines 15-16 and 24-26, Figure 1 - reference numbers 17, 18, 21 and 22);

wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button (See e.g., page 4, line 34 – page 5, line 2, page 5, line 34-page 6, line 2, Figures 1 and 2).

VI. GROUND(S) OF REJECTION TO BE REVIEWED ON APPEAL

The broad issues under consideration are:

1. Whether independent claim 1 is improperly rejected under 35 U.S.C. §102(b) as being unpatentable over US Patent No. 5,383,166 (Gallay).
2. Whether independent claim 1 is improperly rejected under 35 U.S.C. §112 first paragraph as failing to comply with the written description requirement.
3. Whether the drawings are properly objected to under 37 CFR 1.83(a).

VII. ARGUMENTS

A. Summary of Rejection(s) of Record

1. Rejection of claim 1 under 35 U.S.C. § 102(b)

The rejection of claim 1 under 35 U.S.C. §102(b) set forth in the final office action of November 26, 2012 (the rejection) is based on US Patent No. 5,383, 166 (Gallay). In this regard, the rejection (at pp. 2-3 of the final office action) alleges that Gallay discloses a control device which is a push button connection (see figures 1-2) comprising a push button (13), mounted on a driving part (20) being rotatable to the push button (13) which further comprises a bore (internal space of element 11b or 15) with a bottom surface (near 14), which the bore surrounds a protrusion (21 /25) on the driving part (20), which the protrusion (21 /25) has a top surface (top of 25), and wherein a pivot bearing (25/26/11b) is formed between the bottom surface and the top surface (top of 25). Figures 1 and 2 of Gallay are reproduced below with the relevant reference numbers circled:

Fig. 1

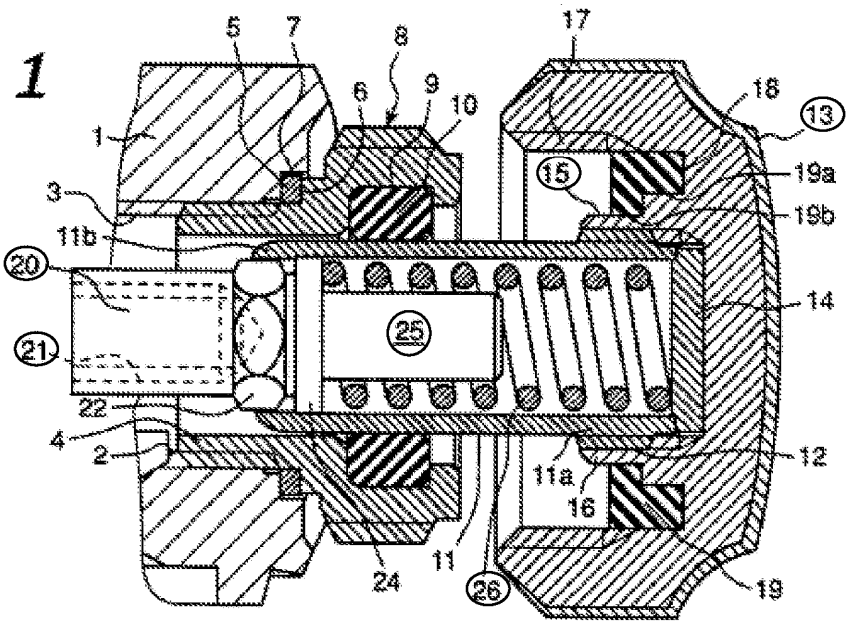
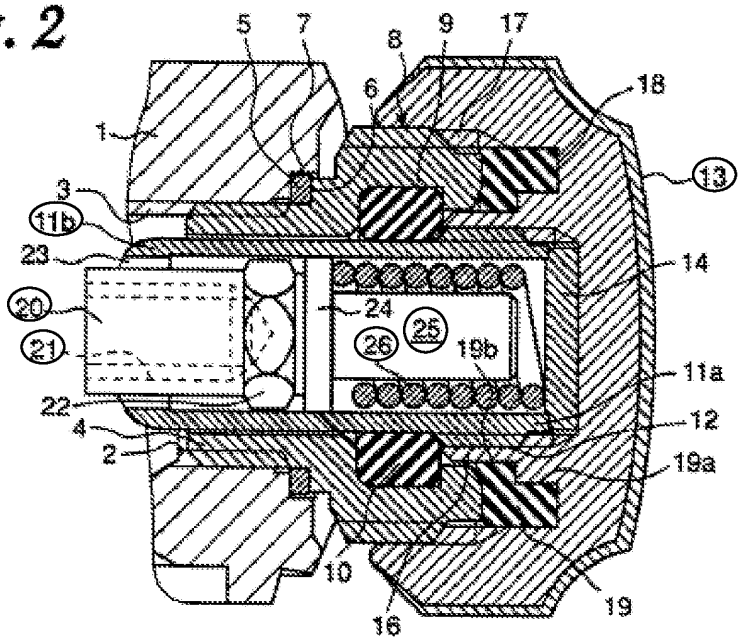

5
7
8
17
6
9
10
18
13
1
15
19a
3
19b
11b
20
14
25
21
22
4
2
12
11a
16
24
11
26
19

Fig. 2


5
7
8
9
17
6
18
1
13
3
11b
23
14
20
24
25
26
19b
21
11a
22
12
4
2
19a
10
19
16

2. Rejection of claim 1 under 35 U.S.C. § 112, 1st Paragraph

Claim 1 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The final office action states that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the phrase "wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button" is allegedly not described in enough specificity to understand what structures and operational elements on the driving part causes the driving part to rotate relative to the push button, (when the user presses the button and directs force to the driving part).

3. Drawings Objection under 37 CFR 1.83(a)

The drawings were objected to under 37 CFR 1.83(a) as not showing every feature of the invention specified in the claims. In particular the final office action states that the phrase "wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button" as recited in claim 1 is not shown in the drawings.

B. Citation of Authority

Under 35 U.S.C. § 102, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631,2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "[A]n invention is anticipated if the same device, including all the claim limitations, is shown in a single prior art

reference. Every element of the claimed invention must be literally present, arranged as in the claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236 (Fed.Cir. 1989) (citing Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888, 894 (Fed. Cir. 1984); Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 771-72 (Fed. Cir. 1983)). "[A]bsence from the reference of any claimed element negates anticipation." Kloster Speedsteel AB v. Crucible, Inc., 793 F.2d 1565, 1571 (Fed. Cir. 1986).

Under 35 U.S.C. § 112, 1st paragraph a patent specification must describe the claimed invention in sufficient detail to allow a person having ordinary skill in the art to reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. An applicant may show possession of the invention as claimed using such descriptive means as words, structures, figures, diagrams that fully set forth the claimed invention. See, e.g., Pfaff v. Wells, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" Enzo Biochem, 323 F.3d at 963, 63 USPQ2d at 1613. An applicant may incorporate subject matter by reference. 37 C.F.R 1.57. Even "essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication. Essential material may include material that is

necessary to provide a written description of the claimed invention as required by the 35 U.S.C. 112, 1st paragraph. 37 C.F.R 1.57(c)(1).

Under 37 CFR 1.83(a), the drawings in a nonprovisional application must show every feature of the invention specified in the claims. However, conventional features disclosed in the description and claims, where their detailed illustration is not essential for a proper understanding of the invention, should be illustrated in the drawing in the form of a graphical drawing symbol or a labeled representation.

C. Claim 1 is Not Properly Rejected Under 35 U.S.C. §102(b) as Being Anticipated by Gallay

Gallay is directed to "a water tight control device for a watch, for example for winding up the watch or setting the time or date." Gallay Col 1, lines 6-8. This type of device typically includes "a crown with a central cavity surrounded by an annular cavity, [and] a watertight seal arranged in the annular cavity." Gallay Col 1, lines 9-11. Claim 1 of the subject application is directed to a push button connection for an injection device which minimizes the forces a user must apply to inject a dose. See page 1, lines 26-27. These two devices are directed to different purposes and accordingly have different structures. Gallay lacks a pivot bearing formed between the bottom surface of the push button and the top surface of the driving part. For at least this reason, claim 1 is patentable over the Gallay reference.

In more detail, claim 1 is directed to a push button connection for an injection device. An example of such a device is shown in the drawings. Figures 3 and 4 are reproduced below. The relevant reference numbers are circled.

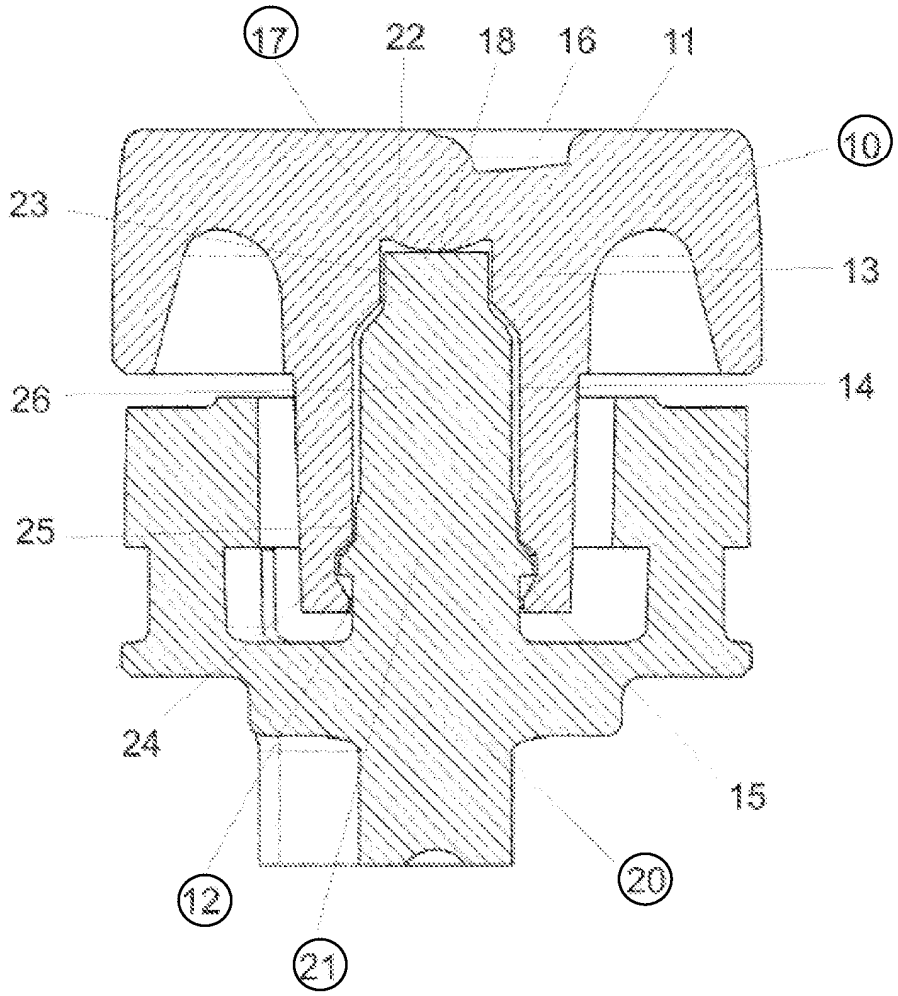
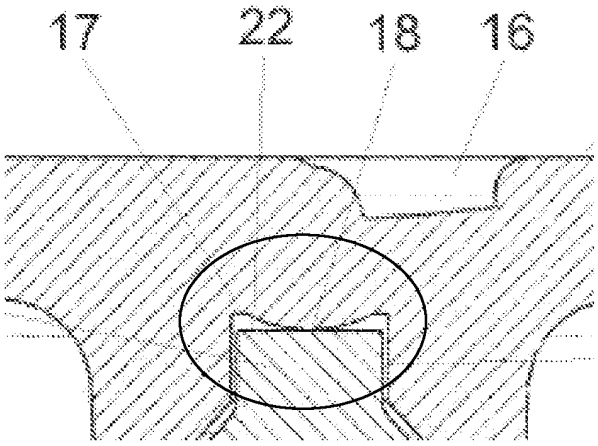


Fig. 1

The device includes a push button (10) mountable on a driving part (20). The driving part (20) is rotatable relative to the push button (10) (See e.g., page 4, lines 26-29, Figure 1 - reference numbers 10 and 20). The push button (10) further comprises a bore (12) with a bottom surface (17) (See e.g., page 5, lines 4-7 and 12-13, Figure 1 - reference numbers 12 and 17). The bore (12) surrounds a protrusion (21) on the driving part (20) (See e.g., page 5, lines 15-16, Figure 1 - reference

numbers 12, 20 and 21). The protrusion (21) has a top surface (22) and wherein a pivot bearing is formed between the bottom surface (17) and the top surface (22) (See e.g., page 5, lines 15-16 and 24-26, Figure 1 - reference numbers 17, 18, 21 and 22). When a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button (See e.g., page 4, line 34 – page 5, line 2, page 5, line 34-page 6, line 2, Figures 1 and 2).

A more detailed view of the pivot bearing shown in Figure 1 is set out below:

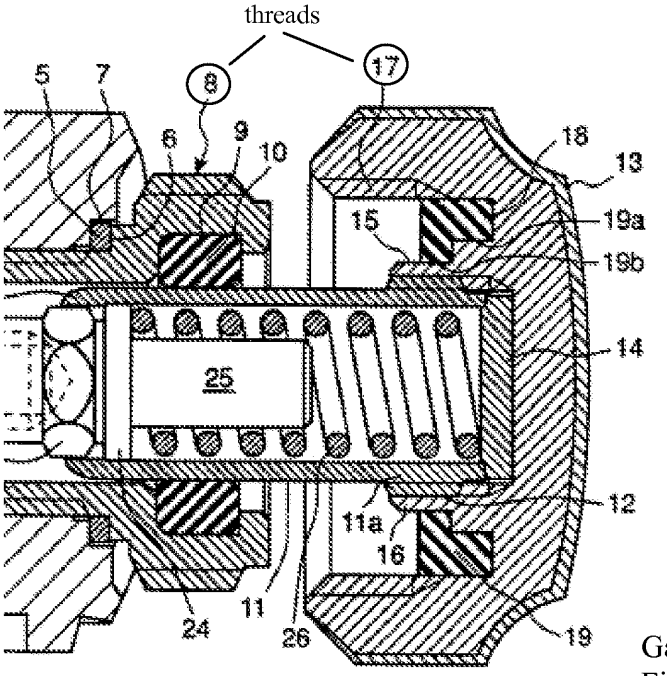


In this example, the "bottom surface 17 of the bore 12 is formed with a raised pointer forming a pivot 18." See page 5, lines 12-13. As noted in the application as filed, "[w]hen a user pushes on the injection button, the force applied is directed to the forward movement of the driving part, however, since the push button and the driving part rotate relatively to each other a friction between these rotating parts will occur." See page 1, lines 29-32. The pivot bearing recited in claim 1 minimizes the friction and the forces a user must apply to inject a dose. Gallay is directed to a completely different application and therefor lacks a pivot bearing as recited in claim 1.

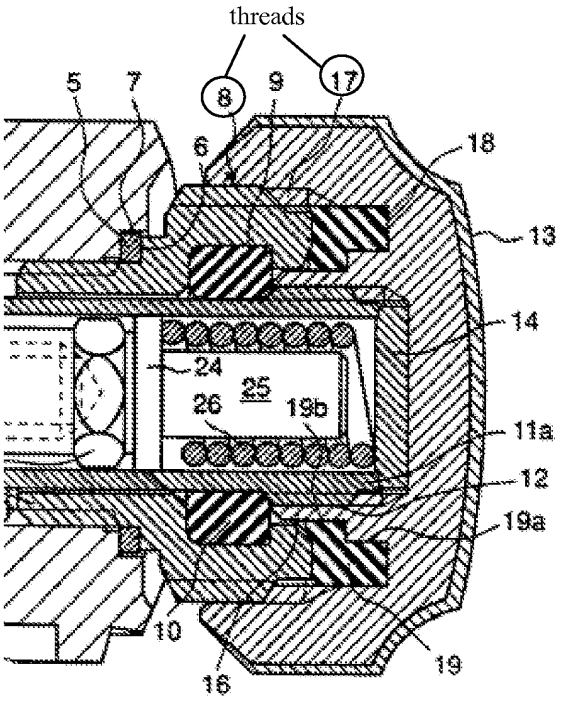
As noted above, Gallay is directed to "a water tight control device for a watch, for example for winding up the watch or setting the time or date." Gallay Col 1, lines 6-8. This type of device typically includes "a crown with a central cavity surrounded by an annular cavity, [and] a watertight seal arranged in the annular cavity." In the rejection, the crown 13 is equated to the push button and the coupling member 20 is equated to the driving part. The cylindrical part 25, coil spring 26, and end 11b of sleeve 11 are identified as forming a pivot bearing. A general description of the operation of a water tight watch crown as recited in Gallay is in order.

Operation of a watch crown is well known. In general, the crown is movable between at least two positions. For example, the crown is pulled out to set the time and pressed in once the time is set. As noted above, the crown disclosed in Gallay is waterproof. In order to achieve this, the crown engages a threaded portion of the watch case so that when the crown is effectively in the "pressed in" position, the waterproof seal surrounding the watch stem is compressed (this is also very well known). Gallay is directed to an improvement in this seal and lacks any disclosure with respect to a pivot bearing formed between the bottom surface of the crown and the top surface of the coupling member.

Gallay expressly states that crown is formed with an annular cavity 15 and the lateral external wall of the annular cavity 15 is provided with a thread 17, which is complementary to the thread of the lateral external face 8 of the widened part of the tube 4. See the highlighted portion of Figures 1 and 2 below. Figure 1 shows the crown in the extended position (unscrewed). Figure 2 shows the crown in the screwed in, position.



Gallay
Figure 1



Gallay
Figure 2

It is readily apparent that as the watch crown 13 is depressed and screwed in, threads 8 and 17 are engaged. Once the crown is screwed all the way in, the threads provide compressive force on the seal 19. This provides a waterproof seal. See Col 2, line 66 - col 3, line 4, Col 3, lines 7-16. In light of this, it is also apparent that Gallay cannot have a pivot bearing formed between the bottom surface of the crown and the top surface of the coupling member. The function of the pivot bearing recited in claim 1 is to reduce frictional forces between the push button and the driving part in an injection pen as the user presses the push button towards the driving part. There is no corresponding bearing in Gallay since it is not required, i.e., there is no need to reduce frictional forces when the user presses on the crown. Instead, the crown is formed with a cavity with a threaded lateral external wall to control the movement of the crown as it moves towards the coupling member. If the user were to press on the crown, the threads 8 and 17 would bear the forces. These threads as well as the cylindrical part 25, coil spring 26, and end 11b of sleeve 11 (identified in the rejection as forming a pivot bearing) do not form a pivot bearing between the bottom surface of the crown and the top surface of the coupling member as recited in claim 1. For at least these reasons claim 1 is allowable over Gallay.

D. Claim 1 is Not Properly Rejected Under 35 U.S.C. §112, 1st paragraph

Claim 1 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The final office action states that the claim limitation of "wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button" is not described in enough specificity to understand what structures and operational elements on the driving part causes the driving part to rotate

relative to the push button,(when the user presses the button and directs force to the driving part).

The specification cites US Patent No. 6,235,004 and US Patent No. 7,427,275 in the background portion. The specification also expressly states "[a]ll references, including publications, patent applications, and patents, cited herein are incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein." See page 3, lines 16-19. Even if the subject matter recited in US Patent No. 6,235,004 and US Patent No. 7,427,275 is considered essential, it is properly incorporated by reference under 37 C.F.R 1.57.

Claim 1 is directed to an improvement in the push button connection for an injection device. The specific mechanism for actually operating an injection pen is not claimed. A person having ordinary skill in the art is well versed as to how such devices operate. For this reason, the rejection under 35 USC 112, first paragraph is misplaced. To the extent there is any question as to how such devices operate, US Patent No. 6,235,004 (the '004 patent) and US Patent No. 7,427,275 (the '275 patent) provide a detailed description and drawings that show the structure required to cause the driving part to rotate relative to the push button in an injection pen. For example in '004 patent, injection button 23 and drum 17 rotate with respect to each other when the injection button is pressed. See Col 7, lines 17-21. The structure for driving the drum is disclosed throughout the '004 patent specification. For at least these reasons, claim 1 complies with the written description requirement under 35 U.S.C. 112, first paragraph.

E. The Drawings are not Properly Objected To Under 37 CFR 1.83

The general rule under 37 CFR 1.83(a) is that drawings in a nonprovisional application must show every feature of the invention specified in the claims. However, conventional features disclosed in the description and claims where their detailed illustration is not essential for a proper understanding of the invention, should be illustrated in the drawing in the form of a graphical drawing symbol or a labeled representation.

As explained above, claim 1 is directed to an improvement in the push button connection for an injection device. The specific mechanism for actually operating an injection pen is not claimed. A person having ordinary skill in the art is well versed as to how such devices operate. The phrase "wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button" as recited in claim 1 provides context under which the claimed pivot bearing operates. The specifics of how the driving part is rotated is not essential for a proper understanding of the invention since it relates to operation of a typical injection pen such as the type disclosed in US Patent No. 6,235,004 (incorporated by reference and discussed above). Appellants note that Figure 2 (reproduced below) provides graphical drawing symbols that represent the forces during rotational movements between the push button and driving part. These graphical drawing symbols provide for a proper understanding of the invention in accordance with 37 CFR 1.83(a).

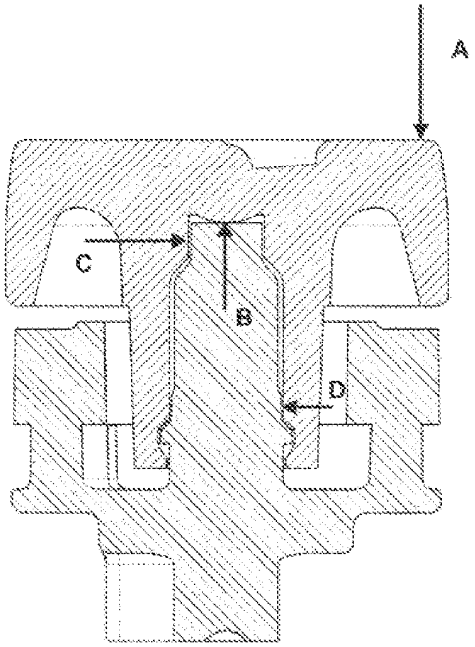


Fig. 2

See also page 5, line 31 – page 6, line 5 describing the forces that occur when the user presses on the push button and the driving part rotates relative to the push button. To the extent additional drawings are required for a proper understanding of the invention , these drawings are provided by the patents that are incorporated by reference. For at least these reasons, the drawings as originally filed are compliant with 37 CFR 1.83(a) and no drawing corrections are required.

VIII. CONCLUSION

Appellant respectfully submits that for at least all of the foregoing reasons, the Office Action fails to particularly point out how Gallay discloses every element of the rejected claim. Appellant has also demonstrated that rejected claim 1 passes muster under 35 U.S.C. §112, first paragraph and 37 CFR 1.83(a). The Board is, therefore, respectfully requested to reverse the Examiner's decision to finally reject claim 1 and to allow the application to issue in its present form.

Respectfully submitted,

Date: July 25, 2013

By: /Marc A. Began, Reg. No. 48,829/

Marc A. Began, Reg. No. 48,829
Novo Nordisk Inc.
Customer Number 23650
(609) 987-5800

Use the following customer number for all correspondence regarding this application.
23650

CLAIMS APPENDIX

1. A push button connection for an injection device comprising:

a push button mountable on a driving part being rotatable relatively to the push button and which push button further comprises a bore with a bottom surface and which bore surrounds a protrusion on the driving part which protrusion has a top surface and wherein a pivot bearing is formed between the bottom surface and the top surface, wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button.

Claims 2-8. (Cancelled)

EVIDENCE APPENDIX

US Patent No. 6,235,004

US Patent No. 7,427,275

RELATED PROCEEDINGS APPENDIX

None

Attorney Docket No. 7543.204-US Application No. 12/525,976

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: HANSEN, Torben Stroem et al. Conf. No.: 2853

Application No.: 12/525,976 Group Art Unit: 3763

Filed: December 16, 2009 Examiner: GRAY, Phillip A.

For: Injection Button

REPLY BRIEF UNDER 37 C.F.R. § 41.41

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Appeal Brief - Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

This Reply Brief pursuant to 37 CFR § 41.41 is presented in response to the Examiner's Answer dated November 20, 2013.

This Reply Brief is submitted by January 20, 2014, and should be entered and considered as of right because it is filed within two months of the Notification Date of the Examiner's Answer.

Although no fees are believed necessary, should any fees be required, the Commissioner is hereby authorized to charge any required fees or refund excess payments to Novo Nordisk Inc. Deposit Account No. 14-1447.

Claim 1 is currently pending. All other claims have been canceled to expedite the appeal.

I. REPLY:

The Examiner's Answer (p. 5) notes that (emphasis added by Appellant):

> The claim language of "wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button . . ." is a functional limitation. It is well established that a recitation with respect to the manner in which an apparatus is intended to be employed, i.e., a

> functional limitation, does not impose any structural limitation upon the claimed apparatus which differentiates it from a prior art reference disclosing the structural limitation of the claim. Where the prior ar is inherently capable of performing the function described in a functional limitation, such functional limitation does not define the claimed apparatus over the prior art.

In response, Appellant respectfully disagrees. And respectfully submit the Examiner's rejection is incorrect for several reasons. First, the Examiner fails to show how each and every element of the claim is present in Gallay. He argues that it is appropriate to ignore some elements recited in the claim by stating that they are merely functional limitations. Of course, even functional limitations must be considered during Examination. Second, the Examiner misinterprets Gallay and argues that the bearing element in the claim is satisfied by a seal in Gallay under the doctrine of inherency. A seal is not inherently a bearing. Finally, the Examiner does not explain how the "pivot" limitation in "pivot bearing" is fulfilled by the Gallay disclosure.

The Examiner's rejection must be overturned because he incorrectly ignores the functional limitations in the claim and mistakenly assumes patent law treats functional limitations in the same way as statements of intended use. It is black letter law that all limitations of a claim must be considered, even functional limitations. As the court held in *In re Exherd*, 176 USPQ (CCPA 1973), "there is nothing inherently wrong in defining something by what it does rather than by what it is." In his reply, the examiner is confusing statements of intended use with functional limitations. See bottom of page 2 of the Examiner's answer where he states that the applicants "only positively claim the 'push button' and its ability to have the functional limitation (or intended use) of wherein when a user presses on the push button the force is direct toward the driving part and wherein the driving part rotates relative to the push button." By using the parenthetical (or intended use) the Examiner is thus admitting that he deems functional limitations to be the same as intended uses. *See* also page 5 of the Examiner's answer where he states "Examiner is reading these as function type or intended use limitations. (Again, confusing functional limitations with statements of intended use). This is wrong as a matter of law.

A functional limitation must be evaluated and considered, just like any other claim limitation "for what it conveys to one of ordinary skill in the pertinent art." *See* MPEP 2173.05(g). "A functional limitation is an attempt to define something by what it does, rather than by what it is." *See In re Swinehart* 429 F.2d 210 (CCPA 1971). That is exactly the case here, where the claim requires rotation between the button and the driving part and the formation of a pivot bearing between the two parts.

Moreover, the definition of a bearing is a machine part in which another part turns. (*See* http://www.merriam-webster.com/dictionary/bearing). The claim plainly recites that a bearing (more specifically, a pivot bearing) is part of the invention, i.e., it is a claim limitation. Therefore, since the claim requires a bearing --and a bearing, by definition involves rotation-- the requirement of rotation between the button and the driving part is implicitly present, as well as explicitly present, in the claim. There is no logical way to read the claim without realizing that the claim requires rotation between two parts when an axial force is exerted on the button. Indeed, why else would there be a bearing between the two parts that rotate, if not to facilitate the rotation?

Finally, in *In re Jasinski* (Fed Cir 2013) the Federal Circuit held that when the functional limitation goes to the heart of the invention, it must be considered. That is exactly the case here. A complete read of the instant specification --which the claims must be read in view of-- clearly shows that the claimed invention is drawn to a pivot bearing in an injection device. Injection devices are well known and virtually all modern injection devices operate by transforming axial movement into rotational motions, as is described in claim 1. (*See* the multiple patents incorporated by reference into the instant patent application). It is absolutely indisputable that one of ordinary skill in the art -- reading the patent as a whole-- would understand that the claim is directed to the bearing in the push button mechanism of an injection pen and involves having a driving part rotate when the injection button is pressed. As such, one of ordinary skill would never understand how the sealed wrist watch crown of Gallay could anticipate claim 1, since Gallay does not contain the rotational limitation of claim 1.

The Examiner's rejection must also be overturned because he has not shown how Gallay supplies the limitation of a pivot bearing. It is indisputable that Gallay disclose a seal for a wrist watch crown. The Examiner admits as much but then incorrectly applies the doctrine of inherency to argue that the seal necessarily could function as a pivot bearing, as is required by claim 1. Prior art inherently anticipates a claim only if the missing element or feature would be necessarily present or the natural result of following what the prior art teaches to persons of ordinary skill in the art. *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). It is not sufficient if the result only possibly or probably results from the practice of the prior art. *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1349 (Fed. Cir. 2004). Moreover, "[a]n invitation to investigate is not an inherent disclosure." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004). Nothing in Gallay indicates to one of skill in the art that the disclosed sealed crown system is inherently capable of rotating relative to a driving part when the crown is pressed inward. Indeed, the Examiner defines the bottom surface in Gallay 15 and the top surface 25 as forming a pivot bearing. But Gallay itself describe element 14 as a seal. (Gallay Col 2, lines 59-63). A seal is a substance, especially an adhesive agent such as wax or putty, used to close or secure something or to prevent seepage of moisture or air. *See* http://www.thefreedictionary.com/seal. A seal is not a bearing. And there is no way that one of ordinary skill in the art would not recognize that a seal necessarily and naturally be the equivalent of a bearing.

Moreover, common sense dictates that Gallay is not inherently capable of performing the function of the invention as claimed. Anyone who has ever used a watch with a crown (the subject of Gallay) knows that pressing on the crown and rotation of the crown are different operations and do not occur simultaneously. One pulls on the crown to set a watch. There is no rotation of the crown relative to a driven part when the crown is pressed. Nothing in Gallay suggests that its seal could form a pivot bearing between a driving part and the button itself, as is required by claim 1. Why would it? Gallay is a watch crown not a push button.

Finally, even if the Board determines that Gallay's seal is a bearing. It is clearly not a pivot bearing. The Examiner has not explained how Gallay creates a pivot bearing. The

examiner completely ignores the term "pivot" in "pivot bearing" and provides no arguments whatsoever how the Gallay watch crown is a "pivot bearing." This reason alone is sufficient to reverse the Examiner's rejection.

With respect to the other rejection based on section 112 and the rejection based on the drawings, applicants rely upon their submissions in the opening brief in this appeal and do not find it necessary to reargue those herein.

II. CONCLUSION

Appellant respectfully submits that for at least all of the foregoing reasons, the Examiner fails to particularly point out how Gallay anticipates claim 1, inherently or explicitly. The Board is, therefore, respectfully requested to reverse the Examiner's decision to finally reject claims1 and to allow the application to issue in its present form.

Respectfully submitted,

Date: January 16, 2014

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

23650
PATENT TRADEMARK OFFICE

Exhibit E

Attorney Docket No.: 5472.220-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Steenfeldt-Jensen et al.

Serial No.: 10/442,855 Group Art Unit: 3763

Filed: May 21, 2003 Examiner: Williams, Catherine Serke

For: Injection Syringe Confirmation No.: 3829

Amendment in a REISSUE Application

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

Sir:

In Response to the Office Action of June 22, 2007, please amend the reissue application as follows:

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 9 of this paper.

Conclusion is at page 12 of this paper.

IN THE CLAIMS:

Please amend the claims to read as follows:

1. (Amended) A medication delivery pen comprising:

a housing having proximal and distal ends and including a holder for containing a cartridge containing a medication to be delivered through a conduit connected to the cartridge,

a piston rod having a not circular cross-section and an outer thread, and

a piston rod drive for driving said piston rod in a distal direction inside the cartridge, said piston rod drive including a first part rotatably mounted within said housing and mating with the not circular cross-section of said piston rod, and a second part integral with said housing and having an internal thread mating the thread of said piston rod to form a [self-locking] thread connection, wherein rotation of said first part in a first direction relative to said second part drives said piston rod in a distal direction; and

a one-way coupling comprising:

a) an annular ring of equally spaced internal ratchet notches situated on the inside of said housing, which internal notches have a steep front edge and a ramp shaped trailing edge,

b) a pawl surrounding said piston rod and having at least a pair of resilient arms, each arm having a free end, said pawl being connected with said first part of said piston rod drive, and

c) means situated on said free end of each arm for engaging in the internal ratchet notches of said annular ring, which means abuts said steep front edge of said internal notches, thereby preventing said pawl body from rotating in one direction relatively to said housing, the prevented direction being one by which the piston rod would be transported in a proximal direction.

2. (Original) A medication delivery pen according to claim 1, wherein said two or more arms are disposed with the same relative spacing around the circumference of said pawl.

3. (Original) A medication delivery pen according to claim 1, wherein said steep front edges of said internal notches on opposite sides of said annular ring are parallel to each other.

4. (Original) A medication delivery pen according to claim 1, wherein said arms extend circumferentially from a body portion of said pawl and wherein said means situated on said free end of each arm is the end-surface of the arm lying circumferentially opposite said pawl and abutting said steep front edge of said internal notches.

5. (Original) A medication delivery pen according to claim 1, wherein said arms extend circumferentially from said pawl body and wherein said means situated on said free end of each arm includes a protrusion.

6. (Amended) A medication delivery pen comprising:

a housing having proximal and distal ends and including a holder for containing a cartridge containing a medication to be delivered through a conduit connected to said cartridge,

a piston rod having a not circular cross-section and an outer thread, and

a piston rod drive for driving said piston rod in a distal direction inside the cartridge, said piston rod drive including a first part having an internal thread mating the thread of said piston rod to form a [self-locking] thread connection, and a second part integral with said housing and mating with the not circular cross-section of said piston rod, wherein rotation of said first part in a first direction relative to said second part drives the piston rod in a distal direction; and

a one-way coupling comprising:

a) an annular ring of equally spaced internal ratchet notches situated on the inside of said housing, which internal notches have a steep front edge and a ramp shaped trailing edge,

b) a pawl surrounding said piston rod and having at least a pair of resilient arms, each arm having a free end, said pawl being connected with said first part of said piston rod drive, and

c) means situated on said free end of each arm for engaging in the internal ratchet notches of said annular ring, which means abuts said steep front edge of the internal notches, thereby preventing said pawl body from rotating in one direction relatively to said housing, the prevented direction being one by which the piston rod would be transported in a proximal direction.

7. (Original) A medication delivery pen according to claim 6, wherein said two or more arms are disposed with the same relative spacing around the circumference of said pawl.

8. (Original) A medication delivery pen according to claim 6, wherein said steep front edges of said internal notches on opposite sides of said annular ring are parallel to each other.

9. (Original) A medication delivery pen according to claim 6, wherein said arms extend circumferentially from a body portion of said pawl and wherein said means situated on said free end of each arm is the end-surface of the arm lying circumferentially opposite said pawl and abutting said steep front edges of said internal notches.

10. (Original) A medication delivery pen according to claim 6, wherein said arms extends circumferentially from said pawl body and wherein said means situated on said free end of each arm includes a protrusion.

11. (Amended) A medication delivery pen comprising:

a housing having proximal and distal ends and including a holder for containing a cartridge containing a medication to be delivered through a conduit connected to said cartridge,

a piston rod having a not circular cross-section and an outer thread, and

a piston rod drive for driving said piston rod in a distal direction inside the cartridge, said piston rod drive including a first part having an internal thread mating the thread of said piston rod to form a [self-locking] thread connection, a second part mating with the not circular cross-

section of said piston rod, wherein said first and second parts are rotatable relative to one another to drive the piston rod in an axial direction; and

a one-way coupling comprising:

a) an annular ring member of equally spaced internal ratchet notches, and

b) a pawl member having at least a pair of resilient arms, each arm having a free end for engaging said ratchet notches so as to allow rotation between said ring and said pawl in a first rotational direction and prevent rotation between said ring and said pawl in a second rotational direction, wherein said members are coupled between said housing and said piston rod drive such that rotation between said members in said first rotational direction causes the piston rod to move in a distal direction, and such that said members prevent movement of said piston rod in said proximal direction.

12. (Twice Amended) An injection device comprising:

a housing for holding a cartridge of medication, the housing having a distal end and a proximal end;

a threaded rotatable piston rod (6) having a not-circular cross-section;

a piston rod drive [means] comprised of:

a first rotatable part that engages the not-circular cross-section of the piston rod so as to allow rotation of the piston rod to accompany rotation of the first part while allowing the piston rod to move proximally and distally with respect to the first part;

a second part that engages the threads on the piston rod and is fixed in the housing, thereby causing the piston rod to move distally when the piston rod is rotated in a first direction and proximally when the piston rod is rotated in a second direction; and

a one way coupling [means] for allowing the first part to rotate in the first direction and thereby drive piston rod to move distally but prevents the piston rod from rotating in the second direction that [which] would cause the piston rod to move proximally.

13. (New) A dose injecting apparatus for an injection device that comprises a cartridge (**89**) of medication from which multiple dose of medication are apportioned and a dose scale drum means (**17**) for indicating the size of a set dose and for indicating that the apportioned set dose has been delivered; the dose injecting apparatus comprising:
a rotatable piston rod (**6**) that rotates only during injecting of medication, wherein the rotatable piston rod comprises a distal portion having an external thread (**7**) disposed thereon and wherein the piston rod has a proximal portion opposite the distal portion;
a first part comprised of a rotatable tubular member (**26,23,33,45,85**) that engages and causes the rotatable piston rod (**6**) to rotate during injection of medication;
a second non-rotatable part (**4,40**) fixed to a housing (**1**), the second part (**4,40**) having an internal thread (**5**) engaging the thread (**7**) on the distal portion of the rotatable piston rod (**6**) so that when the rotatable piston rod (**6**) rotates it screws thru the internal thread (**5**) of the non-rotating second part (**4,40**); and wherein during injection of medication:
(i) the piston rod rotates only in one direction, that direction being one that induces the piston rod to move axially in a distal, medication expelling direction and not in a direction that would induce the piston rod to move in a proximal direction, and
(ii) the piston rod advances distally to expel medication as a result of the screwed engagement of the thread (**7**) on the distal portion of the piston rod (**6**) with the internal thread (**5**) of the non-rotatable part (**4, 40**).

14. (New) The dose injecting apparatus of claim 13, wherein the proximal portion of the piston rod contains a helical thread (**37**) that is different than the thread (**7**) on the distal portion and wherein the tubular member has in its interior a corresponding helical thread (**36**) that engages the helical thread (**37**) on the proximal portion of the piston rod, and wherein the threaded engagement between the tubular member and the thread on the

proximal portion of the piston rod cause the rotation of the piston rod during injecting of medication.

15. (New) The dose injecting apparatus of claim 13, wherein the tubular member has a non-circular interior that engages a non-circular portion of the piston rod so that when the tubular member rotates during injection of medication, it rotates the the piston rod.

16. (New) The dose injecting apparatus of claim 15, wherein the tubular member has a thread (**47**) on it outer surface.

REMARKS

BROADENING REISSUE

This is a broadening reissue application. Applicants intend to claim their invention more broadly than they have previously done. This application was filed within two years of issuance of the patent from which it is a reissue. Accordingly, the claims here are much broader in scope than the claims of the patent that originally issued and the Examiner should consider this new scope, which is limited only by the explicit language of the claims. The Examiner should **not** assume that these claims have scope similar to those previously patented or previously presented in this or any other application claiming the same priority applications as the instant application.

Accordingly, the Examiner should examine these claims anew and conduct a full search and examination and not rely upon any previous searches or examinations. The Examiner should not assume that the specification limits the claims, and should not assume that the claims contain any limitation not explicitly recited therein. The Examiner is urged to give the claims the broadest possible meaning under applicable statutes and case law when examining them for patentability and to consider each element on only each element of the claims when examining them. Where means plus function language is used, it is the intent of the applicants to invoke 35 USC 112 6th paragraph. Where such means plus function language is not present, applicants do not desire to invoke 35 USC 112 6th paragraph.

CONFORMANCE WITH REISSUE RULES FOR AMENDMENTS TO CLAIMS

Claim 12 has been underlined to conform with the rules regarding amendments in reissue applications.

SUPPORT FOR NEW CLAIMS

Claims 13-16 have been added to claim unique, novel and non-obvious aspects of one of the invention described in the application and to broaden the scope of protection conferred by any patent issuing with the new claims. Support for the elements of claim 13 can be found in Figures 3,7,8,13,14, and 17 and the corresponding text at col. 7 line 48 thru col. 8 line 34, for example.

Applicants have inserted reference numerals into the claims in order to show where support for each element can be found in the written description of the patent. It is appropriate to include reference numerals (See MPEP 608.01(m).

Claims 14 is supported by Figure 8 and the corresponding text at col. 7 lines 56-65, for example.

Claim 15 is supported by Figure 17 and the corresponding text at col. 8 lines 45-63 and col. 11 lines 15-17, for example.

Claim 16 is supported by Figure 13 and the corresponding text at col. 8 lines 45-63, for example.

NO IMPLICIT OR EXPLICIT DISCLAIMER OR DISAVOWAL OF CLAIM SCOPE

Applicants note that they are not limiting their invention to the particular embodiments shown in the figures by including reference numerals. (See MPEP 608.01(m)). And are not limiting the claims to inventions previously patented or applied for in this or any parent to the present application. The claims require **only those elements explicitly set forth therein** and does **not require elements not explicitly recited therein**. The Examiner should assume that applicants have purposely excluded any element that is not expressly recited in the claim. The new claims are **not** limited by the particular structures shown in the figures that correspond to the reference numerals used in the claims. These figures and structures merely show an example of the claimed embodiment and demonstrate support for the claim language. Those of ordinary skill in the art will recognize that the claimed invention may be embodied in manners other than that shown in the figures or described in the text and still be within the scope of the claimed subject matter of this patent application.

Accordingly, the figures may show more elements than would be necessary to infringe the pending claims. Indeed, the claims are broader in scope than the figures shown in the patent and would cover embodiments that are not identical to the figures or lack elements shown in the figures so long as those elements are not explicitly recited in the language of the claims.

ACCOMPANYING INFORMATION DISCLOSURE STATEMENT

Finally Applicants note that several other broadening reissues from US Patent 6235004 are pending and applicants would be willing to merge those pending reissues with the instant reissue applications. These applications are cited in the supplemental IDS filed in December 2007, just prior to submission of this paper.

REQUEST FOR AN IN PERSON INTERVIEW

In the event that the Examiner does not believe that all claims are in condition for allowance, applicants respectfully request that the Examiner contact the undersigned attorney in order to set up an in person interview.

CONCLUSION

Applicants respectfully submit that all claims are in condition for allowance and request early action to that end is requested after a new and complete search and examinatopm. The Commissioner is hereby authorized to charge any fees (including but not limited to fees for extensions of time or fees for additional claims or multiple dependent claims, etc.) in connection with this paper or this application, and to credit any overpayments, to Deposit Account No. 14-1447. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: December 20, 2007

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23650
PATENT TRADEMARK OFFICE

Attorney Docket No.: 6036.209-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Klitgaard et al. Group Art Unit: 3744

Application No.: 11/122211 Examiner: Gilbert, Andrew

Filed: May 4, 2005

For: Dose Setting Limiter

AMENDMENT IN A
REISSUE APPLICATION

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

Sir:

In response to the Office Action of November 7, 2008, kindly amend the application as set forth below.

Amendments to the claims begin on page 2 of this paper

Remarks begin on page 6 of this paper

Conclusion is at page 36 of this paper

IN THE CLAIMS:

Please amend the claims to read as follows:

1. (Amended) A limiting mechanism that prevents setting of a dose that exceeds the injectable amount of liquid left in a cartridge of an injection device wherein a dose is set by rotating a dose setting member relative to a driver and away from a fixed stop in the injection device, and the dose is injected by pressing an injection button which [rotating] rotates back the dose setting member which during this rotation carries the driver with it to rotate this driver which moves the piston rod forward, wherein the driver is provided with a track having a length which is related to the total injectable amount of medicament in the cartridge and which track is engaged by a track follower coupled to the dose setting member to follow rotation of this dose setting member and wherein the driver is disk shaped and the track has a spiral shape which is engaged by the track follower which is flexibly coupled to the dose setting member so that the track follower can be moved radially when it follows the track of the driver element.

2-16 (Cancelled)

17. (New) A dose setting limiter assembly that prevents the setting of a dose which exceeds the remaining injectable amount of medication in a multiple dose cartridge in an injection device which comprises: a cylindrical dose setting member (30) having an outer wall provided with a helical groove (29) which allows the dose setting member to be screwed out of the injection device and away from an initial position when the dose setting member is rotated during dose setting and screwed into the device and toward the initial position to reduce the size of a set dose, wherein during injection of the set dose the dose setting member (30) is pressed back into the device and as a result of the helical groove (29) it rotates back toward the initial position;

wherein the dose setting limiter assembly comprises:

(i) a helical track (33) disposed on the outer surface of a hollow cylindrical driver (31) that drives a separate piston rod forward; and

(ii) a follower (32) that engages the helical track (33); wherein the follower moves along the helical track (33) when the dose setting member is rotated during dose setting; but wherein the follower does not move along the track during injection of the set dose, wherein the injection of the set dose is carried out by pressing an injection button which: (i) presses the dose setting member back into the device, and (ii) to cause the dose setting member to rotate back to the initial position, wherein the rotation back is cause by the helical groove (29) on the dose setting member;

wherein the position of the follower along the track is indicative of the total sum of the set and injected doses; and

wherein the total length of the helical track that the follower can move along corresponds to the amount of injectable medication in the cartridge; and

wherein the follower abuts a stop at the end of the track during dose setting before the dose setting element can be rotated to dial up a dose that would exceed the injectable amount of medication remaining in the cartridge.

18. (New) The dose setting limiter assembly of claim 17, wherein when the follower abuts the stop at the end of the track during dialing up of a dose the dose setting member cannot be rotated further to increase the size of the dose.

19. (New) The dose limiter assembly of claim 18, wherein the follower is a nut like element and the helical track (33) is a thread and wherein the follower engages the thread.

20. (New) The dose limiter assembly of claim 19 wherien the driver, the helical grove, the helical track and the dose setting member are oriented so that they are all coaxial.

21. (New) An injection device dose setting member, piston rod driver, and dose setting limiter assembly, which operates with an injection device housing and prevents the setting of a dose that exceeds the injectable amount of medication remaining in a multiple dose cartridge;

wherein the dose limiter assembly comprises a rotatable hollow cylindrical dose setting member (30) containing a threaded groove (29) on its outer surface that cooperates with a housing thread so that the dose setting member screws out of the housing during setting of a dose when it is rotated, screws back into the housing to reduce the size of a set dose when it is rotated back and screws back into the housing when an injection button is pressed; a hollow cylindrical driver (31) that is coaxial with the dose setting member (29), a helical track (33) disposed on the outer surface of the driver (31); wherein the helical track has a length that corresponds to the injectable amount of medication in the cartridge; wherein the dose limiter assembly comprises a follower (32) that engages the helical track (33) and moves along the helical track (33) when the dose setting member is rotated during dose setting but that remains in a fixed position on the helical track (33) when the dose setting member is rotated back when the injection button is pressed during injecting of medication, and wherein the distance the follower moves during dose setting corresponds to the size of the set dose and wherein the follower (32) abuts a stop at the end of the helical track when an attempt is made to rotate the dose setting member during dose setting that would result in a dose being set that exceeds the remaining injectable amount of medication in the cartridge.

22 (New) The assembly of claim 21, wherein the dose setting member is prevented from rotating to increase the size of a set dose when the follower hits the stop.

23. (New) The assembly of claim 21, wherein the track on the driver forms a thread and follower comprises a nut like element that threadly engages the thread.

24. (New) The assembly of claim 22, wherein the track on the driver forms a thread and the follower comprises a nut like element that threadly engages the thread.

25. (New) An injection device dose limiter assembly for use with both

1. a rotatable helical dose setting member, which threadly engages an injection device housing element so that (i) when it is rotated to set the size of a dose it screws out of an injection device housing, (ii) when it is rotated back to reduce the size of a set dose it screws back into the housing, and (iii) when an injecton button is pressed during injecting of medication the dose setting member

is pressed back into the housing and rotates back,
and with

2. a hollow cylindrical piston rod driver that drives a separate piston rod during injection of the set dose;

wherein the dose limiter prevents the setting of a dose that is larger than the injectable amount of medication remaining in a multi dose cartridge and
wherein the dose limiter assembly comprises:

a helical track disposed on the outside of the driver; and
a follower that moves along the track during dose setting but remains stationary with respect to the helical track during dose injecting when an injection button is pressed which causes the dose setting member to be screwed back into the housing; wherein the length of the track that the follower is capable of moving along corresponds to the injectable amount of medication in an injection device multiple dose cartridge; and
wherein during dose setting:
the follower moves a distance along the track that corresponds to the size of the dose being set; and
wherein the follower abuts a stop before the size of the set dose exceeds the injectable amount of medication remaining in the cartridge.

26. (New) The assembly of claims 17, 21, or 25, wherein the follower abuts the stop when the size of the set dose equals the injectable amount of medication remaining in the cartridge.

27. (New) The assembly of claims 17, 21, or 25 wherein the helical track has a length adapted to ensure that the follower stops advancing when the size of a set dose is equal to that remaining for injection.

28. (New) The assembly of claims 1, 17, 21, or 25, wherein the injection button moves a distance proportional to, but a number of times greater than, the distance a piston in the cartridge moves during delivery of the set dose during dose injecting.

REMARKS

Terminal Disclaimers Filed Herewith

To advance prosecution, terminal disclaimers are submitted herewith to overcome the obviousness type double patenting rejections, even though applicants do not believe that such rejections are appropriate. Applicants' attorney notes that these terminal disclaimers were previously filed but for some reason had not been entered. They are submitted again and Applicants respectfully request entry of the terminal disclaimer this time. Should there be a problem with these terminal disclaimers, the Examiner should contact the Applicants' attorney via telephone or email immediately so that prosecution of this reissue may be advanced as soon as possible.

Claim Amendments

Applicants have amended the claims as suggested by the Examiner in the November 14, 2008 interview at the USPTO and to address the Examiner's objections in the previous office action. The formatting complies with Patent Office rules for Reissue applications.

In particular, claim 17 has been amended, as suggested by the Examiner at the November 14th interview, to define that "rotate back" during injection means that the dose setting member be rotated back toward the position it was at prior to when it was rotated to set a dose. Applicants' attorney believes that this new language only clarifies what had already existed in the claims. Support for this language can be found in the Abstract, the specification at column 2 lines 6-18, Column 4 lines 21-23 and lines 39-40 and lines 45-48 and the original claims. Claim 17 has also been reformatted to make examination easier.

Since this is a reissue, the amendments to the claims conform with the MPEP requirements and patent office rules. However, in order that the Examiner can better understand the changes in claims 17, 21, and 25, they are reproduced below with the some of the major additions underlined and deletions noted in the margin.[1]

[1] The Examiner should of course read and examine each claim in its entirety since applicants desire issuance of only the best possible and most enforceable claims. It is noted that the claims define the subject matter of the invention. The terms of the claims should be given their broadest ordinary and plain meaning when examining them and when construing them for purposes of infringement. Nothing should be read into the claims.

17. (New) A dose setting limiter assembly that prevents the setting of a dose which exceeds the remaining injectable amount of medication in a multiple dose cartridge in an injection device which comprises; a cylindrical dose setting member {30} having an outer wall provided with a helical groove {29} which allows the dose setting member to be screwed out of the injection device and away from an initial position when the dose setting member is rotated during dose setting and screwed into the device and toward the initial position to reduce the size of a set dose, wherein during injection of the set dose the dose setting member {30} is pressed back into the device and as a result of the helical groove {29} it rotates back toward the initial position;

wherein the dose setting limiter assembly comprises:

(i) a helical track {33} disposed on the outer surface of a hollow cylindrical driver {31} that drives a separate piston rod forward; and

(ii) a follower {32} that engages the helical track {33}; wherein the follower moves along the helical track {33} when the dose setting member is rotated during dose setting; but wherein the follower does not move along the track during injection of the set dose, wherein the injection of the set dose is carried out by pressing an injection button which: (i) presses the dose setting member back into the device, and (ii) to cause the dose setting member to rotate back to the initial position, wherein the rotation back is cause by the helical groove (29) on the dose setting member;

wherein the position of the follower along the track is indicative of the total sum of the set and injected doses; and

wherein the total length of the helical track that the follower can move along corresponds to the amount of injectable medication in the cartridge; and

wherein the follower abuts a stop at the end of the track during dose setting before the dose setting element can be rotated to dial up a dose that would exceed the injectable amount of medication remaining in the cartridge.

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21. (New) An injection device dose setting member, piston rod driver, and dose setting limiter assembly, which operates with an injection device housing and prevents the setting of a dose that exceeds the injectable amount of medication remaining in a multiple dose cartridge, wherein the dose limiter assembly comprises a rotatable hollow cylindrical dose setting member {30} containing a threaded groove {29} on its outer surface that cooperates with a housing

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thread so that the dose setting member screws out of the housing during setting of a dose when it is rotated, screws back into the housing to reduce the size of a set dose when it is rotated back and screws back into the housing when an injection button is pressed; a hollow cylindrical driver (31) that is coaxial with the dose setting member (29), a helical track (33) disposed on the outer surface of the driver (31); wherein the helical track has a length that corresponds to the injectable amount of medication in the cartridge; wherein the dose limiter assembly comprises a follower (32) that engages the helical track (33) and moves along the helical track (33) when the dose setting member is rotated during dose setting but that remains in a fixed position on the helical track (33) when the dose setting member is rotated back when the injection button is pressed during injecting of medication, and wherein the distance the follower moves during dose setting corresponds to the size of the set dose and wherein the follower (32) abuts a stop at the end of the helical track when an attempt is made to rotate the dose setting member during dose setting that would result in a dose being set that exceeds the remaining injectable amount of medication in the cartridge.

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25. An injection device dose limiter assembly for use with both a rotatable helical dose setting member, which threadly engages an injection device housing element so that (i) when it is rotated to set the size of a dose it screws out of an injection device housing, (ii) when it is rotated back to reduce the size of a set dose it screws back into the housing, and (iii) when an injecton button is pressed during injecting of medication the dose setting member is pressed back into the housing and rotates back, and with a hollow cylindrical piston rod driver that drives a separate piston rod during injection of the set dose; wherein the dose limiter prevents the setting of a dose that is larger than the injectable amount of medication remaining in a multi dose cartridge and wherein the dose limiter assembly comprises: a helical track disposed on the outside of the driver; and a follower that moves along the track during dose setting but remains stationary with respect to the helical track during dose injecting when an injection button is pressed which causes the dose setting member to be screwed back into the housing; wherein the length of the track that the follower is capable of moving along corresponds to the injectable amount of medication in an injection device multiple dose cartridge; and wherein during dose setting the follower moves a distance along the track that corresponds to the size of the dose being set; and wherein the follower abuts a stop before the size of the set dose exceeds the injectable amount of medication remaining in the cartridge.

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Applicants have also amended claim 1 to add the explicit requirement that an injection button be pressed and that the purpose of the limiter is to prevent setting of a dose that exceeds the injectable amount of medication remaining. Support for this amendment can be found throughout the specification, *see e.g* column 3, line 55 and column 2 Summary of the Invention. In addition, Applicants have added a new dependent claim 28, which is supported by the specification. (*See e.g.*, column 1 lines 45-67). Minor amendments have also been made to some of the other claims, including an amendment to claim 25 wherein the phrase "stationary on" has been changed to "stationary with respect to." In addition in claims 21 and 25, amount of "injectable medication" has been change to "injectable amount of medication" or "remaining amount of injectable medication." This makes clear that the purpose of the invention is to prevent the setting of a dose that is larger than the amount in the cartridge that is available for injection. Of course, some residual amount will always remain in the cartridge, however that amount is not available for injection. Also in claim 25, an amendment now makes clear that the track is disposed on the outside of the driver instead of "about the driver." *See* Figure 3 for support for this amendment. Additionally, in claim 25 the word "element" has been added after housing to clarify that the dose setting member need only engage something associated with the housing.[2] These amendments merely clarify the claims and attempt to make them easier to read and understand. In claim 27 "to be injected" has been replaced with "for injection." And in claim 26, "injectable"has been inserted bedfore amount and deleted in from of "medication."

Overview/Background

Applicants' attorney wishes to thank the Examiner for the hour long interview on November 14, 2008 at 10 am. The interview was very constructive in that Applicants' attorney was able to demonstrate how the presently claimed invention can be used with commercial products, such as the FlexPen® product by Novo Nordisk, assignee of the instant application, as well as the commercial product Solsotar® by Sanofi-Aventis. As was noted at the in-

[2] For example, and without limitation, the dose setting member could engage a single unitary housing or it could engage an element associated with a single unit housing, such as a piece that snaps into or fits into another piece that houses something. Arguably such a piece that snaps into or fits into another housing piece would still be part of a housing, but to avoid all doubt, applicants have added this footnote to broadly define housing as including multi-component housings. Indeed, even a single unitary housing can be manufactured from several components that are fitted together so long as in use it houses something or functions as a housing.

terview, there is ongoing litigation in the USA and in Germany regarding intellectual property rights owned by Novo Nordisk and the use of certain technology by Sanofi-Aventis in the Solostar® device. These litigations include a litigation related to a Novo Nordisk owned German utility model and an EP patent owned by Novo Nordisk that claims a dose limiter mechanism. Additionally, a nullity proceeding on the German utility model is pending in Germany. Should the Examiner request, Applicants can provider further details on these litigations.[3]

35 USC Section 102 Rejections of the Previous Office Action

In the previous Office Action, the Examiner has rejected claims 17-27 under 35 USC 102 based upon four documents. In all cases, the Examiner has asserted that each of the four documents anticipate the claims. Applicant's attorney respectfully submits that the Examiner has not made out a prima facie case of anticipation. None of the reference taken alone or in combination for that matter would render the pending claim unpatentable under 35 USC 102 or under 35 USC 103. And therefore the rejections should be withdrawn. Indeed, Applicants believe that all claims are in condition for allowance and respectfully request reconsideration and immediate allowance of the pending claims.

As is apparent from the Examiner's rejections, it seems that one of the fundamental aspects of the claimed invention is not understood by the Examiner. That is, the dose limiting device of the present invention works in an injection device where a dose is set by rotating a dose setting member in one direction and wherein during injection, the dose setting member rotates back toward its initial pre-dose setting postiionewhen an injection button is pressed.[4]

[3]As Applicants' attorney discussed with the Examiner, Sanofi-Aventis's lawyers have made allegations that a dose limiter for a pen syringe was previous invented by a consultant, named Bernard Sams, working for Novo Nordisk in the 1990s. Some information on this is provided in the litigation documents submitted in a previously submitted IDS. *See e.g.,* Declaration of Bernard Sams. *But compare* with the pending claim language.

[4] It should be noted that the manner in which one configures the pen to operate, e.g., the interconnections of the dose setting member and driver and piston rod are not important or relevant for the claims and there are numerous ways that the driver may be driven and numerous ways that the piston rod may be driven by the driver. All such ways that are known by those of ordinary skill in the art are within the scope of the claims so long as each element of the claim is present. Applicants' attorney notes that there are several commercially available products that use the claimed invention. Indeed, as was demonstrated to the Examiner at the interview with Applicants' attorney on November 14, 2008, the present invention is well-suited for use in the commercial product FlexPen® manufactured by the assignee of this reissue application, as well as, in a device configured in a manner such as the device Solostar®, which is manufactured by Sanofi-Aventis and is commercially available in the U.S.A. Both products use the invention as claimed and both were demonstrated to the Examiner during the interview on the 14th of November. During that interview, the Examiner indicated that he understood how the

Also, during an injection operation, a disk shaped or hollow, cylindrical piston rod driver drives a ***separate piston rod*** to expel the dose from the cartridge (2) in the device. An important aspect of the invention is to prevent a rotatable dose setting member from being rotated to a position that would set a dose that is larger than that what remains in the pen during the setting of a dose setting[5]. *See e.g.,* claims 18 and 22. For example, if a pen syringe only has 20 units of insulin, it is desirable to prevent a user from setting a 30 unit dose as the pen would not be capable of delivering the set dose and the user might not realize that he did not get the entire set dose. In some cases it is very desirable to prevent a user from dialing up a dose that is larger than the number of units remaining in the pen that can be injected.

What is claimed in at least some of the claims is the interaction of a follower along a track on a hollow cylindrical piston rod driver that drives the ***separate piston rod*** and how the follower moves relative to the track (or the track relative to the follower), during dose setting and the interaction of the follower along the track during injecting when, as in one aspect of the injecting operation, the dose setting member rotates back as a result of being pressed back into the device.

The invention accomplishes a dose limiting aspect that prevents the dialing up of dose that is larger than the quantity of medication remaining in the device, by allowing a follower to move relative to a track (or a track to move relative to a follower) during setting and adjusting of a dose and to remain fixed along the track, i.e., track dose not move relative or the follower or the follower does not mover relative to the track, during an injection operation, which by definition is the pressing of an injection button and no more. As the follower moves along the track (or the track along the follower) only during dose setting, it acts as a summation machine for the set and injected doses. Thus, the length which the follower can move along the track (or track along the follower) defines the volume of the drug that re-

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claimed invention operated in the FlexPen® and Solostar® devices. Applicants' attorney notes that Flexpen® corresponds to one of the embodiments in the Steenfeldt-Jensen patent. The Solostar® device's operation is detailed further in the litigation materials submitted in the IDS in this application. In short, the Solostar device uses an axially displaceable driver to drive a rotating two threaded piston rod. *See also* Published US App. Ser. Nos. 10/790866 and 11/520598, which Applicants' attorney believes describes the basic operation of at least the Solostar ®device. The beauty of applicants invention is that it is well-suited for pen syringe systems with virtually all types of cylindrical drivers (*e.g.,* drivers that rotate and/or axially move to drive a piston rod), and can be adapted for use with such drivers by inclusion of a track and follower in the manner claimed.

[5] Of course, the claims are not limited to anything but that which is explicitly required on their faces. No limitations should be read into the claims from the specification or elsewhere. The specification is merely illustrative of one or few embodiments. The basic concept of the claims is applicable to multiple embodiments regardless of any language in the specification.

mains in the pen syringe cartridge that is available to be injected.[6] One important aspect of the claims is that if a dose setting member rotates back as a result of being pressed into the device, the relative position of the follower on the track remains fixed, but if the member is rotated as a result of dose setting or dose adjustment the follower does move along the track (or the track along the follower) thus adjusting the sum of the set and injected doses as compared to the total injectable amount of medication in the device whenever a dose is set. When an attempt is made to set a dose that exceeds the remaining amount of medication in the device, the dose setting member is prevented from rotating. *See e.g.*, claims 18 and 22. Thus, before an injection is made, the user will know that the device does not contain enough medication to deliver the desired dose.

With the above background to the pending claims, Applicant's attorney sets forth the below some of the reasons why the Examiner's application of the four cited documents to the pending claims fails to render them unpatentable. Applicant's attorney has only set forth the reasoning with respect to claim 17 but as the remaining claims also require the same elements, which are also not present in the four cited documents, that reasoning applies to the remaining rejected claims as well. In addition, the table below set forth, with citation to the documents, some of the more significant errors in relying upon these documents to reject the pending claims. It does not necessarily include every flaw in the Examiner's reasons for rejecting the claims. Applicants respectfully submit that the Examiner must withdraw the previous rejections based on the following arguments.

Applicable law of Anticipation

Applicants' attorney notes that in order to reject the pending claims based on prior art, the prior art must show a device having the structure defined by the claims and the components must operate in the manner required by the pending claims. Thus, function and structure are important aspects, as is how the structures cooperate with each other. The prior art does not explicitly or inherently show the recited structures interacting in operation in the manner required by the claims.

[6] Of course, the total volume in the cartridge will always be somewhat larger than the amount available for injection since not every last drop of medication in the cartridge can be pressed out. The invention is directed at the useable or injectable amount of medication and not the absolute total volume of that which is placed into a cartridge by a manufacturer.

Summary of Arguments with Respect to Harris, Chanoch, Balkwill, and Steenfeldt-Jensen

Set forth below is a summary of key reasons why the Examiner's rejections based on the four cited documents must be withdrawn. For a detailed explanation with citations to the reference the Examiner should and must consider the detailed tables that also appear further below.

Rejections based on Harris must be withdrawn

The Examiner's rejection with respect to Harris must be withdrawn for the numerous reasons identified in the below table, which includes the fact that element 86, identified by the Examiner as the dose setting element, does not rotate during injection as is required by the claim. There is no helical groove on an outer wall of element 86. The Examiner's assertion that 94 is a threaded groove that engages a housing thread 19 is not supported by Harris, which defines 94 as a tang and 19 has a linear groove. Moreover, the follower 104 of Harris does not move along a helical track during dose setting. After a dose is set, 104 is ***then*** set by the user and then remains in place during dose setting and dose adjusting. The claims explicitly require that the follower move during rotation of the dose setting element during dose setting. (*See e.g.*, claim 17 which requires "wherein the follower moves along the helical track (33) ***WHEN*** **the dose setting member is rotated** ***DURING*** dose setting.").

Additionally, the Examiner is wrong in stating that the length of 106 corresponds to the amount of drug in the cartridge. The length of the thread 106 in Harris is does not correspond to the injectable amount of medication in the cartridge, it corresponds to a limitation on the maximum size of a dose a user can set on the device. A user can still set a dose larger than that which is remaining in the cartridge.

Rejections based on Chanoch must be withdrawn

The Examiner's rejection in view of Chanoch must also be withdrawn for numerous reason. Not least is the fact that the Examiner has not pointed to an element in Chanoch that is a hollow piston rod driver that ***drives a separate piston rod***. The Examiner's assertion that 88 is a hollow piston rod driver with a helical groove on its outer surface reads the requirement that the driver be hollow and **that it drive a separate piston rod** out of the claim. Indeed, element 88 is a piston rod, not a hollow driver that drives a separate piston rod. Moreover, the assertion that element 34 is a follower that moves along the track 94 during dose

setting but remains stationary on the track during injection, ignores the explicity teaching of Chanoch, and if Chanoch were so modified it would be inoperable. It is the rotation of 34 during dosing along thread 94 that causes element 88 to move relative, in an axial manner, to 34. The thread 94 moves along 34 during injection and therefore does not and cannot remain fixed along 34 during injection. The pending claims require that the follower not move along the track during injection. In summary, Chanoch teaches away from the invention.

Rejections based on Balkwill must be withdrawn

The Examiner's rejections based on Balkwill are also flawed for numerous reasons and must be withdrawn. Among them is the fact the Examiner ignores explicity claim limitations that are not shown or even suggested by Balkwill. For Example, the Examiner argues that element 12 is a dose setting member that has a helical groove on its outer wall that causes it to screw out of the device during the setting of a dose. He identifies element 14 as a thread or helical groove. Balkwill himself defines element 14 as an upper body. And element 12 does not contain a helical groove on *its outer wall*. Moreover, as is shown in Figures 1 and 2, ***element 12 does not screw*** out of the device during dose setting, as is required by the claims. And ***12 does not rotate back when it is pressed back into the device*** during injection. Element 12 is never pressed back into the device, as is required in claim 17. While element 22 is pressed back into the device, it does not cause element 12 to rotate when it is pressed back in. Moreover, element 22 does not even rotate when it is pressed back into the device.

Additionally, the Examiner fails to point to a hollow piston rod driver in Balkwill that drives a ***separate piston rod***. Like in Chanoch, the Examiner points to a solid piston rod, element 26, and claims that is a driver for driving a **separate** piston rod. Of course, this impermissibly reads a limitation out of the claim. Indeed, it reads out the "hollow" limitation, as well as the "driver" limitation. In short, element 26 is a solid piston rod, it is not a driver for a **separate** piston rod. If element 26 were deemed to be a piston rod driver, what would it drive? What then is the piston rod? And how is it hollow?

Rejections based on Steenfeldt-Jensen must be withdrawn

The Examiner rejections based on Steenfeldt-Jensen must also be withdrawn if for no other reason that he has failed to identify how Steenfeldt-Jensen prevents the setting of a dose that exceeds the remaining medication in the pen syringe device. In addition, the Examiner once again determines that a solid piston rod, element 6, is a hollow piston rod driver

for **driving a separate piston rod**. He does this notwithstanding the fact that Steenfeldt Jensen explicitly defines element 6 as a piston rod and defines other elements as drivers. (*See* elements 85 in Figure 17, 26 in Figure 2, element 45 in Figure 13). In none of these figures is there a track having a length corresponding to the injectable amount of medication available in the pen.[7] The Examiner has ignored the explicit teaching of Steenfeldt-Jensen that states element 6 is the piston rod. Like in the other rejections, the Examiner ignores the fact that the driver by definition must drive a separate piston rod. Thus, the piston rod cannot be a piston rod driver.

In addition to this fundamental flaw, even if one were to assume the piston rod 6 of Steenfeldt-Jensen were hollow and drives a separate piston rod, Steenfeldt-Jensen would not prevent the setting of a dose that exceeds the amount of medication remaining in the device. The nut 40, which the Examiner deems to be a follower, moves relative to the track 7 on the piston rod 6, only during injection not during dose setting. The pending claims require movement of the track relative to the follower (or the follower relative to the track) during dose setting and no relative movement between the track and follower during dose injecting.

Thus, Steenfeldt-Jensen operates in a manner that is opposite the manner required by the claims and therefore cannot anticipate or render obvious the claims. Indeed, as was demonstrated to the Examiner at the November 14th interview, Steenfeldt-Jensen does not preclude the setting of a dose that would exceed the remaining injectable amount of medication in the pen without the addition of the present invention. Moreover, the Examiner has utterly failed to explain how the dosage setting element in Steenfeldt-Jensen would be prevented from being dialed up to an amount that exceeds the amount of medication remaining in the device. The interaction of the components cited by the Examiner would only become relevant after a dose is set, which is too late in time to prevent the setting of dose that exceeds the amount of medication left in an injection.

[7] To the extent element 47 could be considered a helical track, it does not have a length corresponding to the injectable amount of medication in the pen and the only element that appears to engage 47 is a tubular nut element 48 that moves along 47 during injecting, which of course is the opposite of what is required by the pending claims of this reissue application. Indeed, the pending claims require no relative motion between a follower and a track during dose injecting. For this embodiment of Steenfeldt-Jensen to operate relative motion is needed during injecting. Moreover, as the interaction of 47 and 48 occur after dose setting *and during injecting*, this interaction does not prevent the setting of a dose that exceeds the injectable amount of medication remaining in the pen syringe.

A more detailed explanation of the some of the flaws in thee Examiner's rejections is set forth in the tables below:

Claim 17 (Prior to current amendment)	Examiner's application of **Harris** to the particular elements of claim 17	Reasons why the Examiner's application of Harris does not anticipate Claim 17,
A dose setting limiter that prevent setting of a dose which exceeds the amount of injectable medication in a multiple dose cartridge in an injection device	The Examiner states that Harris discloses an injection device that prevents the setting of a dose that exceeds the injectable amount of medication in a multiple dose cartridge, but does not cite any language in the specification that supports this naked assertion.	The Examiner has failed to point to language citing the required function of the dose limiter and thus the Examiner has not made out a prima facie case of anticipation. Harris discloses an apparatus that allows a user to limit the size of a maximum, not to a limiter that prevents the setting of a dose that exceeds the remaining capacity of the syringe which is what the instant claim of the pending reissue patent application is directed toward, i.e., an embodiment of an invention that prevents a user from setting a dose that is larger than the amount of medication remaining in the device. See pending claim 17 last wherein clause which sttes "wherein the follower abuts a stop at the end of the track during dose setting before the dose setting element can be rotated to dial up dose that would exceed the injectable amount of medication in the cartridge." For example, the Examiner cites no language from Harris that suggests the Harris device would prevent a user from dialing a 34 unit dose when only 20 units remain in the pen. See for example,

		figures 5-9, in which the Harris device is set to allow what appears to be a maximum dose size to 34 units in a pen that is capable of delivering 60 units per dose. But after a user exhaust all but 20 units of medication, the user can still dial up 34 units even though the device does not have 34 units remaining. See also column 4, lines 15-36, which states clearly that "the principle function of the follower 104 is to set a maximum allowable dose where the syringe is going to be used by persons who may have difficulty remembering the proper dosage or may have some other physical disability which does not permit them to appreciate fully the meaning of the indicia." Thus, Harris discloses a limiter that prevents an impaired patient from overdosing rather than a limiter that prevents an impaired patient from under dosing by setting a dose that a device is not capable of giving.
which comprises		
a cylindrical dose setting member 30 having an outer wall provided with a helical groove 29 which allows the dose setting member to be screwed out of the injection device when the dose setting member is rotated during dose setting and screwed inward to reduce the size of a set dose,	The Examiner asserts that Harris discloses a dose setting member 86 having a threaded groove 94. The Examiner asserts that the threaded groove 94 cooperates with a housing thread 19	Element 86 does not have an outer wall with a helical groove. See Figs. 4, 2 and 1. Element 94 is not a groove and is not helical. Nor is it the equivalent of a helical groove. As discussed above and below, 94 is a radial projecting tang and not a threaded groove. See Figure 4 and col-

	so that the dose setting member screws out of the housing during setting of a dose when it is rotated, screws back into the housing to reduce the size of a set dose when it is rotated back.	umn 4 lines 27-30. Moreover, element 19 is a linear groove not a thread. See Harris figure 4 and column 4 lines 27-30. Note that by definition a thread is helical. In fact, 94 and 19 act to prevent rotation and thus cannot cause rotation in the manner claim 17 requires. (See column 4 lines 32-25).
wherein during injection of the set dose the dose setting member 30 is pressed back into the device and as a result of the helical groove 29 it rotates back;	The Examiner identifies element 86 as a dose setting member and asserts that the other claim limitations recited here (e.g., rotates when pressed back, etc) are met by Harris, but he provides no citation to where the Harris patent teaches that the dose setting member rotates back when it is pressed in during injection and where the rotation is a result of a helical groove.	The Examiner's naked assertion that element 86 meets the limitation of the claim is incorrect because element 86 dose not rotate when the injection button is pressed during an injection. See figures 7 and 8. In fact, at column 5, lines 32-35 Harris states clearly the cap 72, which includes elements 86 (see col. 4 lines 12-14) moves linearly. Linear motion is not rotation. And the claim requires rotation. Indeed, the explicit language in Harris is that the tang 94 aids linear movement of the cap with respect to the housing under application of a force normal to the proximal end of the cap. Figure 7 shows the Harris device in a dialed up position with a set dose. See column 6 line 37-55. At this point, two alternative things can be done to the device. Either the element 86 can be rotated back [e.g. to reduce or cancel a set dose] in which case no drug is dispensed (see column 6 lines 39-42), or a

		normal force can be applied to the end of the device (see column 6, lines 42-55) to inject a dose. "It will be noted that with the force F applied to the proximal end 98, the cap 72 and plunger rod 56 have both moved ***linearly*** [i.e., not rotated] through a distance L which is identical to the distance D shown in FIG. 6. The motion of the plunger rod 56 causes forward motion of plunger 36 as shown in FIG. 2 to dispense the liquid within the container 14." See also column 6 lines 47-53. Thus, during injection element 86 does not rotate back. And claim 17 explicitly requires rotation back during injection. In short, the claim requires rotation back of the dose setting member during injection and Harris teaches the opposite, i.e., linear movement during injecting. Moreover, rotation of 86 would not cause dispensing of fluid in the Harris device as it would result in canceling the set dose. No one could reasonably believe 94 is a helical groove on the outer surface. Moreover, element 19 in Harris is a linear groove. 94 and 19 actual act together to prevent rotation. See column 4 lines 32-35 which state 'the tang 94 also aids linear movement of the cap with respect to the housing under the application of a force

		normal to the proximal end 98 of cap 72."
wherein the dose setting limiter assembly comprises:		
(i) a helical track 33 disposed on the outer surface of a hollow cylindrical driver 31	Examiner cites the cap element 100 as the driver	
that drives a separate piston rod forward and		
(ii) a follower 32 that engages the helical track 33; wherein the follower moves along the helical track 33 when the dose setting member is rotated during dose setting; but wherein the follower does not move along the track when the dose setting member is rotated back when an injection button is pressed during injection to press the dose setting member back into the injection device;	Examiner asserts that element 104 is a follower but does not cite language in the Harris patent that satisfies the other requirements for the claimed follower. The examiner makes another naked assertion that the element 104 function in the manner required by the claim elements.	The Examiner's naked assertions about the element 104 are incorrect because Harris does not teach that 104 move along a track ***during*** dose setting when the dose setting member is rotated. Harris teaches that ***first*** a dose is set then a user moves 104 along a track where it will remain. See column 6 lines 25-30. For example, Harris states "the cap 72 can ***first*** be rotated to the desired maximum measured value . . . ***Next*** the follower 104 is rotated." Thus, by Harris's own language 104 is not moved along the track when the dose setting member is rotated ***during dose setting***, it is moved after the dose setting member is rotated during dose setting. (The word "next" in this passage means next in a sequence of events and cannot possibly mean "during" as the pending claims require). See also figure 6 corresponds to the setting of the follower on the track ***after*** setting a dose. Moreover, once 104 is set by a user it does not move along a track when a user next dials a dose during dose setting.

		See column 6, lines 55-65, and column 7 lines 1-5. The point of setting 104 is so that when a dose **is then** set, the set dose cannot exceed the maximum value allowed by 104. As further evidence that Harris teaches the opposite of the claim limitation (which requires that the follower move along the track during dose setting) see column 6, line 37, which states "with the follower 104 set in the position shown in Figure 7, the cap 72 an be rotated back [without expelling a dose]." As is shown in Figure 8 the follower remains in it position on the track during this rotation back. Figure 8 clearly shows that 104 had not moved relative to a track during rotation of 86 to during adjustment of the dose size or cancellation of the dose. See also, column 6 lines 55-65, which state that when it is necessary to again use the syringe, the cap is rotated and the follower now limits the motion which can take place to something significantly less than that which could have been achieved before the follower was moved in Figure 6. Thus, in accordance with these provisions of the Harris patent and the corresponding figures, the follower does not move along the track during dose setting. If it were to move, it would not serve its intended purpose of limiting a dose size to a predetermined value.

wherein the position of the follower along the track is indicative of the total sum of the set and injected doses and	The examiner states that distance the follower moves during the setting of a dose corresponds to the size of the set dose	First, as is discussed above, 104 does not move during setting of a dose. Second, to the extent 104 is moved, the distance it is moved corresponds to a maximum size that a dose can be set. See column 6, lines 15-26. No where does Harris state that 104 moves a distance corresponding to the size of the set dose. (In fact Harris specifically states that the set dose might be less than the distance 104 was previously moved. See column 7 lines 3-5). Moreover once 104 is set, for subsequent doses 104 does not move along a track. In fact, the whole point of 104 is that it remains fixed along the track for both subsequent dose settings. In short, nothing in Harris suggests that when the device is nearly empty, one could not set a dose up to the limit allowed by 104 that is greater than the amount remaining in the pen. For example if 10 units remain in the pen syringe and 104 limits maximum dose size to 15 units, a patient could still set 15 units which would exceed the amount of available medication by 5 units. Thus, this feature of Harris does not prevent the setting of a dose that exceeds the useable amount of medication in the

		device.
wherein the total length of the helical track that the follower can move along corresponds to the amount of injectable medication in the cartridge and wherein the follower abuts a stop at the end of the track during dose setting before the dose setting element can be rotated to dial up a dose that would exceed the injectable amount of medication remaining in the cartridge.	The Examiner states Harris discloses these limitation, but does not provide citation to the specification of Harris.	The Harris specification makes clear that the distance 104 is moved is determined by the user as the largest dose that the device can then be set to. See column 6 lines 15-36. Note that as shown in Figure 7 the follower is set to limit the dose to just under 36 units, for discussion purposes assume please assume the set dose is 34 units. If a user attempted to set a 34 unit dose when only 20 units remained in the syringe the follower would not prevent this. Thus, Harris does not prevent the setting of a dose larger than that which remains in the syringe. 104 and its engagement with a thread do not keep track of the amount of remaining medication in the device and therefore do prevent a user from setting a dose that the device is in capable of delivering. Finally there is no indication whatsoever that the length of the track on which 104 moves is in anyway related to the amount of useable medication in the pen. 104 limits the size of each dose that can be delivered by the syringe.

Claim 17	Examiner's application of **Balkwill** to the particular elements of claim 17	Reasons why Balkwill does not anticipate Claim 17,
A dose setting limiter that prevent setting of a dose which exceeds the amount of injectable medication in a multiple dose cartridge in an injection device		
which comprises		
A cylindrical dose setting member 30 having an outer wall provided with a helical groove 29	The examiner asserts that element 12 is a dose setting member and that element 14 is a threaded groove.	Element 12 does not contain an outer wall with a helical groove. Element 14 is defined as an upper body. See column 9 line 8. Also see Figures 1, 2, and 5b. Moreover, even if the Examiner intended to state that 14a (and not 14) is a threaded groove, the specification teaches that it is a cam molded inside the upper body 14. See column 9 lines 17-18.
which allows the dose setting member to be screwed out of the injection device when the dose setting member is rotated during dose setting and screwed inward to reduce the size of a set dose,	The Examiner asserts that the groove 14 cooperates with a housing thread 18 so that the dose setting member screws of the housing during setting of a dose.	As stated above 14 is not a helical groove. Second, element 12 does not screw out of a housing during dose setting. See Figures 1 and 2 showing 12 being axially fixed during dose setting. Likewise 12 is not screwed inward to reduce the size of a dose. As further evidence that element 12 does not screw, see figure 8 which shows the device after a dose as been set and compare this with figure 7. See also figures 1 and 2.
wherein during injection of the set dose the dose setting member 30 is pressed back into the device and as a result of the helical groove 29 it		Dose setting member 12 is not rotated back as a result of a helical groove. In fact, the dose setting member does not rotate during injection be-

rotates back into the device toward the fixed stop;		cause as stated at column10 lines 53-58 the dose remains displayed subsequent to injection. Moreover, the Balkwill patent states clearly the injection procedure requires three steps: "set to zero, set the dose, make the injection" See column 6 lines 1-5. Thus, the dose setting member in Balkwill dose not rotate during injection because if it did rotate back during an injection, there would be no need to set to zero before the next injection. In addition, element 12 is not pressed back into the device. It has never moved outward from the device and cannot move inward into the device as it is axially fixed. Element 22 moves outward and inward, but that is not a dose setting element as it is not rotated to set a dose. Addtionally, Balkwill states at column 10 lines 53-57 "the dosage to be administered is clearly displayed and **will remain** displayed subsequent to the injection procedure." Thus, element 12 does not rotate back during injecting of the set dose.
wherein the dose setting limiter assembly comprises:		
(i) a helical track 33 disposed on the outer surface of a hollow cylindrical driver 31 that drives a separate piston rod forward and	The Examiner asserts that the piston rod driver is element 26, but he does not state how this drives a separate piston rod. He also asserts element 26c is a helical track. Applicant's attorney will assume that the Examiner means 26d.	Element 26 is clearly not hollow. Moreover and more importantly element 26 is the piston rod in the device. It therefore cannot be both the piston rod driver and drive a separate piston rod.

wherein the position of the follower along the track is indicative of the total sum of the set and injected doses and wherein the total length of the helical track that the follower can move along corresponds to the amount of injectable medication in the cartridge and wherein the follower abuts a stop at the end of the track during dose setting before the dose setting element can be rotated to dial up a dose that would exceed the injectable amount of medication remaining in the cartridge.	The Examiner asserts that element 28 is a follower and that it remains fixed on a track when the dose setting member rotates back when an injection button is pressed.	As element 12, the element that the Examiner states is the dose setting member, does not rotate back during injection, this limitation of the claim is not met by Balkwill. Moreover, as element 26 is a piston rod not a hollow driver that drives a separate piston rod, this limitation is not met. Not only is element 26 not a driver for a separate piston rod, it is not even hollow.

Claim 17	Examiner's application of **Chanoch** to the particular elements of claim 17	Reasons why Chanoch does not anticipate claim 17
A dose setting limiter that prevent setting of a dose which exceeds the amount of injectable medication in a multiple dose cartridge in an injection device		
Which comprises		
A cylindrical dose setting member 30 having an outer wall provided with a helical groove 29 which allows the dose setting member to be screwed out of the injection device away from an initial position when the dose setting member is rotated during dose setting and screwed inward to reduce the size of a set dose, wherein during injection of the set dose: (i) the dose setting member 30 is pressed back into the device and (ii) as a result of the helical groove 29 it rotates back towards an initial position;	Examiner asserts that element 58 is a dose setting member containing a threaded groove 70	
`wherein the dose setting limiter assembly comprises:		
(i) a helical track 33 disposed on the outer surface of a hollow cylindrical driver 31 that drives a separate piston rod forward and	The Examiner asserts that 88 is the driver and the track is the thread 94 but the examiner does not cite any language to support an assertion that 88 drives a separate piston rod.	Element 88 is the piston rod it does not drive a separate piston rod. It cannot be both the piston rod and a driver for a separate piston rod. Moreover, element 88 is not hollow.
(ii) a follower 32 that engages the helical track 33; wherein the follower moves along the helical track 33 when the dose setting member is rotated during dose setting; but wherein the follower does not move along	The Examiner asserts element 34 is a follower and that 34 moves along 94 during dose setting, but does not state how this is possible.	The Examiner is incorrect as Element 34 does not move along a track during setting of a dose. As is stated at column 7 , when a dose is set the nut does not rotate (see also column 7 lines 23-25) and the piston rod dose not

the track when the dose setting member is rotated back when an injection button is pressed during injection to press the dose setting member back into the injection device;	Examiner also states that 34 does not move along 94 during injection but again fails to state how this is possible.	rotate (see column 8 lines 11-13 (stating "rotation of lead screw 88 is prevented by grooves 96 and tabs"), therefore element 34 cannot move along 94 during setting of dose. Moreover, as is stated in columns 7-8 , when the injection button is pressed, rotation of the nut 34 is induced and since rotation of lead screw is prevented and since nut 34 is axially fixed, lead screw advances relative to the nut 34. Thus, during injection the nut moves along or relative to the thread 94. In fact this is what drives the dose from the syringe. In sum, the rotation of nut 94 in combination with a rotationally fixed piston rod 88 drives the piston rod 88 forward. When 88 moves forward it moves relative to 88 and thus track 94 is moved along 34 during injection. This is the opposite of what is claimed in the instant reissue patent application.
wherein the position of the follower along the track is indicative of the total sum of the set and injected doses and wherein the total length of the helical track that the follower can move along corresponds to the amount of injectable medication in the cartridge and wherein the follower abuts a stop at the end of the track during dose setting before the dose setting element can be rotated to dial up a dose that would exceed the injectable amount of	The Examiner asserts that Chanoch teaches that the distance the follower moves during dose setting corresponds to the size of the set dose and that element 34 abuts a stop to prevent the setting of a dose that would exceed the remaining amount of medication in the device.	Even if one were ignore the express teachings of the patent and add to the disclosure in the manner done so by the Examiner, element 34, which the Examiner deemed as a follower, would not abut a stop at the end of thread 94 during dose setting because during dose setting 34 and 88, along with thread 94 do not move relative to each other during dose setting. To the extent 34 might abut a stop along thread 94 it would

medication remaining in the cartridge.		do so during injecting not during do setting.

Claim 17	Examiner's application of **Steenfeldt Jensen** to the particular elements of claim 17	Reasons why Balkwill does not anticapte Claim 17,
A dose setting limiter that prevent setting of a dose which exceeds the amount of injectable medication in a multiple dose cartridge in an injection device	Examiner makes as assertion that Steenfeldt-Jensen contains a dose limiter that prevents the setting of a dose that would exceed the remaining amount of injectable medication in an injection device. He provides no citation to anything in Steenfeldt –Jensen that supports this naked assertion.	The Examiner's naked assertion about the scope of Steenfeldt-Jensen is unsupported. Steenfeldt-Jensen discloses a pen with a gearing where the dose setting member moves a greater distance upon injection than the piston rod. In fact, the embodiments in Steenfeldt-Jensen are in need of the dose limiting mechanism of the present invention. With Steenfeldt-Jensen, it is possible to set a dose on the dose setting element that is larger than the amount remaining in the pen. In fact, the commercial product FlexPen® sold by the assignee of the instant application is based on one of the designs in Steenfeldt-Jensen. (See also, the commercially available product Solostar from Sanofi-Aventis that also employs the invention defined by the claims of this reissue patent application.) One should note however the design of the dose limiter in the instant reissue had to be incorporated into Steenfeldt-Jensen FlexPen in order to achieve a dose limiter that prevents the setting of a dose larger than that which remains in the pen. In sum, Steenfeldt-Jensen does not have a dose limiter that prevents the setting of a

		dose that is larger than the amount of injectable medication remaining in the pen. Applicants note that Steenfeldt-Jensen provides for multiple designs for a geared pen which are suitable for use with the present invention but that does not mean Steenfeldt-Jensen anticipates or renders obvious the claimed invention. It merely provides examples of needs for the present invention, much like an automobile provides a need for improved tires without anticipating or rendering obvious a new tire design.
which comprises		
a cylindrical dose setting member 30 having an outer wall provided with a helical groove 29 which allows the dose setting member to be screwed out of the injection device when the dose setting member is rotated during dose setting and screwed inward to reduce the size of a set dose, wherein during injection of the set dose the dose setting member 30 is pressed back into the device and as a result of the helical groove 29 it rotates back;	Examiner asserts that element 80 is a dose setting member. The examiner asserts that element 80 can be screwed out during dose setting and screwed back in to reduce a dose and rotates back when it is pressed in during an injection.	
wherein the dose setting limiter assembly comprises:		
(i) a helical track 33 disposed on the outer surface of a hollow cylindrical driver 31 that drives a separate piston rod forward and	The Examiner asserts that element 6 is a hollow cylindrical piston rod driver. But the Examiner fails to state how Steenfeldt Jensen discloses that element 6 drives a separate piston rod. The examiner asserts that the helical track is element 7.	Element 6 is defined as a piston rod. Other elements (i.e. not element 6) are defined as possible drivers for piston rods. The Examiner has ignored the express teaching of Steenfeldt-Jensen and supplemented the disclosure by making naked assertions in order to fill the gaps in the

		reference. In sum, element 6 is explicitly defined as a piston rod and therefore cannot be a piston rod driver for driving a separate piston rod. Moreover, there is no indication whatsoever that element 6 is hollow. Hollowness is required by the claim.
(ii) a follower 32 that engages the helical track 33; wherein the follower moves along the helical track 33 when the dose setting member is rotated during dose setting; but wherein the follower does not move along the track when the dose setting member is rotated back when an injection button is pressed during injection to press the dose setting member back into the injection device;	Examiner asserts that element 40 is a follower that moves along a helical track during dose setting.	Element 40 is a nut that is fixed to the housing, It is both rotationally and axially fixed to the housing. Element 6, the piston rod, rotates during injection but does not rotated during dose setting. Thus, since element 40 and 6 are threadly engaged, and neither rotate during dose setting, element 40 cannot move along the thread 7 during dose setting and remain fixed during injection. In sum, Steenfeldt-Jensen teaches the opposite of what the claim requires.
wherein the position of the follower along the track is indicative of the total sum of the set and injected doses and wherein the total length of the helical track that the follower can move along corresponds to the amount of injectable medication in the cartridge and wherein the follower abuts a stop at the end of the track during dose setting before the dose setting element can be rotated to dial up a dose that would exceed the injectable amount of medication remaining in the cartridge.	The Examiner asserts that element 85 is a stop that acts to prevent the setting of a dose that exceeds the amount of medication remaining in the device.	Even if thread 7 were to have a length corresponding to the size of the dose in the cartridge (something the Examiner assumes without citation to the specification), and a element 85 were a stop that engages the nut 40, the device would still allow for a dose that exceeds the amount remaining in the cartridge to be set on the dose setting element 80 because element 85 would only abut nut 40 when the piston rod is being driven forward, i.e. during an injection. The claim requires preventing the setting of a dose

		that exceeds the remaining amount of medication in the pen during dose setting. Thus, even assuming that the Examiner's embellishment of the Steenfeldt-Jensen reference were somehow plausible, the Examiner fails to demonstrate, for example, how the if in the Steenfeldt-Jensen device only 20 units remained in the cartridge, the dose setting element 80 would be prevented from being dialed to 21 units or more. Put simply, even if one were to take the position that 80 and 40 would abut during injection a position which the Examiner has not supported with citation to the specification – the dose setting member would merely stop rotating during the injection. But at this point it would be too late for a user to learn that the injectable amount of medication in the syringe is less than the set dose. In contrast, the claimed invention requires that a dose cannot be set that exceeds the amount of medication left in the syringe thus preventing a user from ever getting into this situation.

Nature and Purpose of this Reissue Application

Applicants note that this is a broadening reissue patent application and that the intent of filing this application was to broaden the claims of the issued patent. Claiming the invention too narrowly is the error that Applicants wish to correct with this Reissue Application. (*See* the reissue oath submitted in this application.) As such, the language of the new claims is broader than what was originally claimed in the original issued patent. The claims are clear on their face and limitations from the specifications should not be read into the claims. Applicant's contend that one of ordinary skill in the art should be able to read the pending claims and understand them without the need to refer to the specification. It is noted that in cases where some of the new claims contain some language that is taken verbatim or nearly verbatim from the specification (or original or previously pending claims) it should be assumed that only that language that is explicitly recited in the claims is required by the claims. Language that is not recited in the current claims that is either in the specification or the original claims or previously pending claims has been intentionally not included in the pending claims by the Applicants so as to broaden their claimed invention as is their right under applicable patent law. In short, reference or inclusion of some language from the specification or old claims or even the file history of the original or reissue application does not mean that other non-included language should be considered when construing the claims. The claims mean only what they say on their face. Nothing else should be read into them when examining them or when construing them for infringement purposes.

Indeed, a purpose of filing this reissue is to claim broadly the concept of providing a track, or threads, on a cylindrical driver that is engaged by a track follower, which moves along the track during dose setting but does not move relative to the track during injection when an injection button is depressed and a dose setting member rotates back toward a zero position during the pressing of the button. As is described in some of the claims, one way to obtain "[t]he limitation of the set dose is obtained by giving threads an appropriate length." Column 2 lines 47-50. That broad concept is embodied in the pending claims. Of course, it is the claims --when interpreted according to the ordinary and plain meaning of the words used therein-- that define the invention. For purposes of determining claims scope for infringement, all the claims require is that at least the element recited therein operate in the manner described in therein.

Finally, to the extent that anything in the specification or the file history of this reissue application or the original patent could in anyway be construed as a disclaimer of claim scope, applicants hereby ***EXPRESSLY RESCIND ANY SUCH DISCLAIMER OF CLAIM SCOPE***. To infringe the claims of this application all that is required is that the elements recited in the claims be present in an accused product and that they operate in the manner described in the claims. Of course, other elements could also be present in the accused product so long as at least the recited elements are present. Indeed, applicants have used the claim language "wherein" and "comprising" for this reason as it is open language and the meaning of these terms is well-known patent law.

CONCLUSION

As discussed at the interview, it is believed that the claims are in condition for allowance, and a determination to that effect is earnestly solicited.

The commissioner is authorized to charge any and all fees in connection with this application, including fees for extensions of time, should such extensions be necessary to the Novo Nordisk Deposit account. 14-1447 and to credit any overpayments to the same.

Respectfully submitted,

Date: November 21, 2008

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