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Datasheet for the decision of 11 November 2022

Case Number: T 0605/20 - 3.3.07

Application Number: 04797453.0

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Language of the proceedings: EN

Title of invention:

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

Patent Proprietor:

NOVO NORDISK A/S

Opponents:

Sandoz AG
Fresenius Kabi Deutschland GmbH
Wittkopp, Alexander
Teva Pharmaceutical Industries Ltd.
Generics (U.K.) Limited
Uexküll & Stolberg
Partnerschaft von Patent- und Rechtsanwälten mbB

Headword:

Peptide formulations/NOVO NORDISK

Relevant legal provisions:
EPC Art. 123(2), 83, 54, 56

Keyword:
Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Novelty - selection invention
Inventive step - formulation of the technical problem

Decisions cited:
T 0971/92, T 1087/15, T 0800/91, T 0116/18, T 0002/81, T 1170/02, T 0249/12

Catchword:
The undesired phenomena observed in the patent with the use of the prior art compositions would not inevitably manifest themselves upon the practical implementation of the teaching of the prior art. The recognition of the relevance of these phenomena should therefore be considered to form part of the technical contribution described in the patent. A specific reference in the formulation of the objective technical problem to the avoidance of these phenomena risks to unfairly direct development towards the claimed solution, which is not permissible in line with the principles as developed in the established jurisprudence (see reasons section 4.2.3).

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Case Number: T 0605/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 November 2022

Appellant: (Opponent 1)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
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Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 11 February 2020 rejecting the opposition filed against European patent No. 1687019 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	L. Basterreix

Summary of Facts and Submissions

I. European patent 1 687 019 ("the patent") was granted on the basis of seventeen claims.

Claim 1 as granted relates to:

"A pharmaceutical formulation comprising the peptide Arg34, Lys26(Nε-(γ-Glu(Nα-hexadecanoyl)))-GLP-1(7-37) and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from 1 mg/ml to 100 mg/ml, and wherein said formulation has a pH of from 7.0 to 10.0."

Dependent claims 3-5 as granted respectively define more specifically that the final concentration of the propylene glycol is from 1 mg/ml to 50 mg/ml, from 5 mg/ml to 25 mg/ml and from 8 mg/ml to 16 mg/ml.

Dependent claim 7 as granted defines the formulation of any preceding claim, wherein said peptide consists of Arg34, Lys26(Nε-(γ-Glu(Nα-hexadecanoyl)))-GLP-1(7-37).

Dependent claim 10 as granted defines that the pH of the formulation is 8.0 to 8.3.

Dependent claim 12 as granted defines the formulation to comprise a preservative in a concentration from 0.1 mg/ml to 20 mg/ml.

The peptide Arg34, Lys26(Nε-(γ-Glu(Nα-hexadecanoyl)))-GLP-1(7-37) is herein further referred to by its present common name "liraglutide".

II. Six oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed.

Opponents O1, O3, O4 and O5 filed appeals against the decision of the opposition division to reject the oppositions.

The opposition division cited *inter alia* the following documents:

D3: WO 03/002136
D4: WO 2005/046716
D6: Handbook of PHARMACEUTICAL EXCIPIENTS, 3rd Edition, 324-328
D7: Am J Hosp Pharm, 1978, 35(11), 1337
D11: Antivir Res, 2001, 50, 117-127
D12: Yakugaku Zasshi, 2003, 123(11), 957-961
D13: Pharm Res, 1991, 8(10), 1258-1263.
D16: WO 95/22560
D18: US 5,981,489
D22: WO 98/005351
D29: WO 02/067989
D31: Modern Pharmaceutics, Fourth Edition, 2002, p. 682
D39: EP 0037043 B1
D47: Am J Hosp Pharm, 1980, 37, 16-22
D48: Handbook of Pharmaceutical Excipients (2009), 6th Edition, 424-428
D49: Declaration of Dorthe Kot Engelund of 4 December 2019, including excerpt from US Pharmacopeia 2003

The opposition division arrived at the following conclusions:

(a) Claim 1 as granted corresponded to claim 1 as originally filed with the further specification of the peptide as liraglutide. Liraglutide had been individually disclosed in the examples and the claims of the application as originally filed. The amounts of propylene glycol as defined in claims 3-5 as granted concerned originally disclosed preferred amounts. The definition in claim 7 as granted that the peptide "consists" of liraglutide was implicit in the original disclosure. The definition of the pH range of 8.0 to 8.3 in claim 10 as granted resulted from a limitation of a broader disclosed range on the basis of a disclosed specific value. The combination of liraglutide, propylene glycol and the amounts of preservative defined in claim 12 as granted was derivable from claims 8 and 9 as originally filed.

The patent as granted did therefore not comprise subject-matter extending beyond the content of the application as originally filed.

(b) The preparation of the defined compositions was straightforward as illustrated by example 3 of the patent. No evidence to the contrary had been presented.

The patent as granted thus satisfied the requirement of Article 83 EPC.

(c) Document D3 did not unambiguously disclose the combination of liraglutide and propylene glycol and

did therefore not anticipate the subject-matter of claim 1 as granted.

Document D3 did not affect the validity of the claimed priority, which was otherwise not contested. Document D4 could therefore not qualify as prior art.

The subject-matter of claim 1 as granted was therefore new over the prior art.

(d) Document D3 represented the closest prior art. The difference between claim 1 of the patent and the disclosure in document D3 concerned the specific combination of liraglutide with propylene glycol.

In view of the data in Table 3 and the tests described in examples 2 and 3 of the patent the problem to be solved was defined as the provision of liraglutide-containing formulations which are associated with reduced deposits.

Neither document D3 nor any of the other cited documents indicated that the isotonic agent mannitol led to the formation of deposits. The patent thus addressed an unrecognised problem which could give rise to patentable subject-matter regardless whether the claimed solution was trivial or not.

Even if the patent was not considered to address an unrecognised problem, the claimed subject-matter would involve an inventive step, because the advantageous effect of propylene glycol could not have been foreseen by the skilled person.

III. In its communication pursuant to Article 15(1) RPBA of 2 March 2022 the Board expressed the preliminary opinion that the patent as granted does not comprise subject-matter extending beyond the content of the application as filed, that the patent as granted sufficiently discloses the claimed invention and that the subject-matter of the claims as granted is new and involves an inventive step over the prior art.

IV. Opponent O3 withdrew its appeal with the letter of 29 March 2022.

Opponent O4 withdrew its appeal with the letter of 21 June 2022.

V. Oral proceedings were held on 11 November 2022 in the form of a videoconference.

VI. The arguments of the appellant-opponents relevant to the present decision are summarized as follows:

- Amendments

  Claims 3-5, 10 and 12 comprised subject-matter extending beyond the content of the application as originally filed in the form of a new combination of the selection of liraglutide as peptide with the definition of concentrations of the propylene glycol, the definition of a pH range or the definition of the presence of a preservative in a particular concentration range.

  The application as filed did furthermore not describe a formulation in which the peptide "consists" of liraglutide as defined in claim 7 as granted.

- Sufficiency

  The limited experimental evidence in the examples of the patent only concerned compositions comprising 14 mg/ml of propylene glycol. The patent did thereby not enable the skilled person to achieve reduced deposits over the whole scope of the claims.

- Novelty

  Document D3 already described a pharmaceutical formulation comprising a modified GLP-1 compound and an isotonic agent in amounts of 1-50 mg/ml having a pH of 7 to 10. Document D3 described liraglutide in a similar manner as the patent as the preferred modified GLP-1 compound by defining this compound exclusively in a single claim and individually highlighting the compound in the description under "Summary of the invention", in the listed 78 typical formulations (see pages 26-35) and the examples (see page 36, lines 27-29, "Compound 1"). The remaining definition of propylene glycol in the patent corresponded to the selection of propylene glycol as the isotonic agent to be used from a single list (see D3, page 18 line 33 to page 19 line 15), which could not establish novelty over the teaching in document D3.

- Inventive step

  Document D3 represented the closest prior art. The difference between the formulation of claim 1 as granted and the exemplified formulations in document D3 concerned the definition of propylene

glycol as the isotonic agent instead of mannitol or glycerol.

(a) Starting from a formulation with mannitol as isotonic agent

It was evident from example 3 of the patent itself that in practice the use of mannitol as described in document D3 inevitably confronts the skilled person with the problem of undesired deposits and clogging of injection devices. It was therefore appropriate to formulate the objective technical problem as how to avoid such formation of deposits and clogging of devices. Such formulation of the objective technical problem was in line with the established jurisprudence regarding "problem inventions" (see Case Law of the Boards of Appeal, 10th Edition, I.D.9.12), according to which the recognition of a problem could affect the assessment of obviousness, but not the formulation of the objective technical problem.

As no improved stability from the use of propylene glycol with respect to mannitol had been substantiated and propylene glycol could not be expected to compromise the stability of the compositions, the formulation of the objective technical problem could not be based on any effect from propylene glycol on the stability of the defined composition. In the context of the assessment of the replacement of mannitol by propylene glycol any improvement from the use of propylene glycol with respect to glycerol would be irrelevant.

The skilled person was aware of the problematic tendency of mannitol towards crystallisation from documents D6, D7, D47 and D48. It would further represent routine practice to identify mannitol as the cause of the problematic deposits. The skilled person would therefore as a matter of obviousness consider the replacement of mannitol by a liquid non-crystallizing isotonic agent in order to avoid deposits and clogging of injection devices due to crystal formation. The fluid state of propylene glycol at relevant temperatures was common knowledge, which was evidenced by document D33. Moreover, the suitability of propylene glycol for use as an isotonic agent was well known from documents D31, D22, D29 and D39 and was actually mentioned in document D3 itself. It was therefore obvious for the skilled person to replace mannitol in the exemplified compositions in document D3 by propylene glycol.

The problem of the formation of deposits and clogging of devices concerned a conventional technical problem, which would be addressed in the course of skilled person's normal activities. In accordance with the established jurisprudence regarding "problem inventions" (see Case Law of the Boards of Appeal, *supra*, I.D.9.12, in particular T 971/92), the recognition of this problem could therefore not contribute to an inventive step.

(b) Starting from a formulation with glycerol as isotonic agent

The patent stated that glycerol did not clog injection needles and, just like propylene glycol, did not cause deposits on filling equipment. It

could therefore not be concluded from the patent that the use of propylene glycol instead of glycerol provided for any improvement in this respect. It was further not evident from the patent that propylene glycol provided for any advantage over glycerol with respect to the stability of the compositions.

Merely as solution to the problem of providing an alternative formulation the claimed compositions comprising propylene glycol would be obvious in view of document D3, which explicitly describes propylene glycol as an alternative isotonic agent.

The recognition of any advantage from the use of propylene glycol over the use of glycerol would require assessment of the plausibility of such advantage in view of the information presented in the patent. The relevance of the referral in G 2/21, which addresses the issue of plausibility of an effect relied upon in support of an inventive step, should therefore be taken into account.

Achieving improved stability by using propylene glycol instead of glycerol would anyway be obvious in view of documents D11, D12 , D13, D16 and D18.

Any problem associated with the occurrence of gel-like drops on the needle as reported in Table 3 of the patent would manifest itself upon mere implementation of the teaching of document D3. As explained in T 1087/15 knowledge of the claimed invention was absolutely necessary in order to formulate the objective technical problem. The problem to be solved could therefore be formulated as how to avoid the occurrence of such drops, even

if the formation of such drops is not mentioned in document D3. In as far as the considerations in T 800/91 suggested differently, these considerations would diverge with respect to the more recent decision in T 1087/15 and would not be applicable in view of the development of the jurisprudence.

Faced with the problem of avoiding the gel-like drops occurring with formulations comprising glycerol as the isotonic agent the skilled person would immediately recognize that the formation of the gel-like drops is associated with the well known viscous character of glycerol. It would be obvious to the skilled person to replace glycerol by propylene glycol to solve such problem, because propylene glycol is explicitly described in document D3 as suitable isotonic agent, whilst the lower viscosity of propylene glycol was part of the common knowledge, which was evidenced by document D33.

The skilled person would actually be in a "one-way street" situation to test propylene glycol for replacing glycerol in view of document D3 and documents D11, D12, D13, D16 and D18.

VII. The arguments of the respondent relevant to the present decision are summarized as follows:

- Amendments

The application as originally filed indicated liraglutide as the preferred peptide, which was for instance evident from the examples and original claim 17, which exclusively defined liraglutide as

the peptide of choice. The application as filed thereby also disclosed formulations in which the patent consisted of liraglutide as defined in claim 7 as granted. The concentrations defined in claims 3-5 as granted were originally described as convergent preferred limitations. The pH range defined in claim 10 resulted from a combination of originally described ranges. The definition of the concentration of the preservative in claim 12 was based on an originally described preferred embodiment. Example 3 provided a pointer towards the combination of the features in claims 3-5, 10 and 12.

The patent as granted did therefore not comprise subject-matter extending beyond the content of the application as originally filed.

- Sufficiency

No serious doubts as to the reproducibility of the claimed invention had been raised.

- Novelty

Document D3 did not present an individualized disclosure of the combination of all the features of claim 1 as granted. The document only described liraglutide as a possible component amongst other modified GLP-1 compounds, the inclusion of an isotonic agent as optional and propylene glycol as possible isotonic agent amongst others. In this context document D3 did not provide any pointer towards the combination of features as defined in claim 1 of the patent and failed in particular to link propylene glycol with a specific concentration

range. On the contrary, the examples in document D3 related exclusively to formulations comprising mannitol or glycerol as isotonic agent and none of the typical formulations mentioned in document D3, which the appellant-opponent 01 relied upon for the first time in its letter of 11 August 2022, actually included propylene glycol.

- Inventive step

As demonstrated by the results in Table 3 and examples 2-3 of the patent the compositions comprising propylene glycol as defined in the claims of the patent instead of mannitol as described in document D3 resulted in the reduced formation of deposits and the reduced clogging of injection devices. The results in Table 3 of the patent also showed the reduced occurrence of gel-like drops from the use of propylene glycol instead of glycerol. The patent further reported that propylene glycol did not affect the physical and chemical stability of liraglutide formulations. Post-published evidence confirmed that propylene glycol allowed for better stability of liraglutide compositions than glycerol.

The formation of deposits and clogging of needles or the occurrence of gel-like drops as demonstrated in the particular experimental set-up disclosed in the patent would not necessarily manifest themselves upon the practical implementation of the teaching of document D3. The formulation of the problem to be solved in terms of the avoidance of such events would therefore unfairly direct development towards the claimed solution. In accordance with established jurisprudence (see Case

Law of the Boards of Appeal, *supra*, I.D.4.2.1, in particular T 800/91) such a formulation of the problem to be solved was not permissible, because it necessarily resulted in hindsight tainting the assessment of obviousness. The problem to be solved should therefore be formulated in more general terms as the provision of liraglutide-containing formulations having improved manufacturability and usability whilst maintaining stability.

Document D3 itself recommended mannitol and glycerol as the preferred isotonic ingredients and provided no suggestion towards any advantage from the use of propylene glycol. The declaration in document D49 confirmed that mannitol was one of the most frequently used isotonicity agents and that problems from using mannitol in formulations comprising liraglutide were not expected. Documents D6, D7, D47 and D48 mentioned the crystallisation of mannitol from highly concentrated solutions and did therefore not provide any relevant information for improving the compositions of document D3, which contain far lower concentrations of mannitol as an isotonic agent. Documents D11-D13, D16 and D18 described the use of propylene glycol in formulations of peptides other than liraglutide. It could not be expected that any stabilizing effect from propylene glycol mentioned in these documents could be extrapolated to compositions comprising liraglutide. These documents did further not provide any suggestion towards the claimed subject-matter as solution to the identified technical problem.

VIII. No substantive submissions were received from opponent 02 and opponent 06 (parties as of right pursuant to Article 107 EPC).

IX. Appellant-opponent O1 and appellant-opponent O5, requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

X. The respondent requested that the appeal be dismissed.

Subsidiarily, the respondent requested that the patent be maintained on the basis of one of auxiliary requests 1-8 as filed with its reply of 20 October 2020.

The respondent further requested that the new submission in the letter of 11 August 2022 by appellant-opponent 01 regarding seventy-eight typical formulations described in document D3 be disregarded.

Reasons for the Decision

Main request, patent as granted

1. Amendments

1.1 In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that the patent as granted did not comprise subject-matter extending beyond the content of the application as originally filed on the basis of the following considerations:

- The application as originally filed seemed to describe liraglutide as the peptide of choice for the defined combination of a peptide and propylene

glycol (see page 8, lines 29-30 and examples 3-4, compare also claim 17 as originally filed).

- The application as originally filed described the ranges of granted claims 3-5 as convergent limitations, which appeared to represent preferred embodiments.

- The definition of the peptide as consisting of liraglutide in dependent claim 7 did not seem to add any further information regarding the peptide to be used.

- In view of the originally disclosed pH sub-ranges 7.3-8.3 (see page 13, lines 22-23; see also claim 7) and 7.2-8.0 (see page 13, lines 18-19) and the disclosed pH value of 8.15 of example 3 and in line with the principles as applied in decisions T 2/81 (section 3), T 1170/02 (sections 4.4-4.5) and T 249/12 (section 3.1.3) the opposition division appeared to have correctly concluded that the pH range of 8.0-8.3 as defined in claim 10 as granted was directly and unambiguously derivable from the original disclosure (see decision under appeal, pages 4-5 section 1.4). Furthermore, example 3 seemed to link this range to the defined combination comprising liraglutide and propylene glycol.

- The application as originally filed specifically described the embodiment involving a preservative in the amounts as defined in claim 12 as granted (see original claims 8-9). Example 3 seemed to link this embodiment to the combination of choice comprising liraglutide and propylene glycol.

1.2 No substantive arguments were submitted by the appellants in response to the Board's preliminary opinion regarding the amendments and at the oral proceedings the appellants relied on their written submissions. Accordingly, the Board confirms the opinion expressed in the communication pursuant to Article 15(1) RPBA that the patent does not comprise subject-matter extending beyond the content of the application as originally filed.

2. Sufficiency

2.1 In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that the patent as granted did not comprise subject-matter extending beyond the content of the application as originally filed. As demonstrated in the examples of the patent, the preparation of a formulation as defined in claim 1 as granted appeared straightforward and no convincing evidence of insufficiency had been presented.

2.2 No substantive arguments were submitted by the appellants in response to the Board's preliminary opinion regarding the requirement of sufficiency and at the oral proceedings the appellants relied on the written submissions. Accordingly, the Board confirms the opinion expressed in the communication pursuant to Article 15(1) RPBA that the patent sufficiently discloses the claimed invention.

3. Novelty

3.1 Document D3 describes pharmaceutical formulations having a pH of 7 to 10 which comprise a modified GLP-1 compound and specifically mentions liraglutide as such modified GLP-1 compound (see D3, under "Summary of

invention", page 3, line 17 to page 4, line 14; see also claims 1 and 25).

Document D3 describes various more specific embodiments, including an embodiment in which the formulation comprises an isotonic agent, wherein the isotonic agent may be selected from a variety of groups of agents, such as polyhydric alcohols, including *inter alia* propylene glycol, or mixtures thereof, but preferably mannitol or glycerol (see D3, page 18, line 33 to page 19, line 9). In further embodiments described in document D3 the isotonic agent is present in a concentration from 1-50 mg/ml, 1-7 mg/ml, 8-16 mg/ml or 17-50 mg/ml (see D3, page 19, lines 10-16). Document D3 also includes dependent claims defining the formulation to comprise an isotonic agent (see D3, claim 13) and the concentration of the isotonic agent as ranging from 1-50 mg/ml (see D3, claim 14).

Document D3 presents a list of further embodiments relating to various different modified GLP-1 compounds, including liraglutide (see D3, page 26, lines 10-27) followed by a list of 78 typical pharmaceutical compositions which all comprise liraglutide in combination with mannitol or glycerol (see D3, page 26, line 28 to page 35, line 29). In the experimental section document D3 presents examples which all comprise liraglutide (see page 36, line 27-28, "Compound 1" and pages 37-45) and which either comprise no isotonic agent (see examples 2-3 and partly examples 5 and 7) or comprise mannitol or glycerol as isotonic agent (see examples 1, 4 and 6 and partly examples 5 and 7).

3.2 Claim 1 as granted defines a pharmaceutical formulation characterized by the following features:

- the presence of liraglutide,

- the presence of propylene glycol in a concentration of 1-100 mg/ml, and

- a pH of from 7.0 to 10.0.

As is evident from section 3.1 above, document D3 discloses formulations comprising liraglutide and having a pH within the same range as defined in claim 1 as granted. In this context the Board observes that the the submission of 11 August 2022 by appellant-opponent 01 relating to the 78 typical formulations in document D3 comprising liraglutide does not represent an amendment to its appeal case, because this submission corresponds to the argument in the statement of grounds of appeal by appellant-opponent 01 that all examples of D3 relate to formulations comprising liraglutide.

However, contrary to the arguments from the appellant-opponents the Board does not consider the subject-matter of claim 1 of the patent to simply result from a straightforward, single selection with respect to the teaching of document D3 involving propylene glycol as the isotonic agent.

As set out in section 3.1 above, document D3 describes the presence of an isotonic agent only as optional. Moreover, whilst the specific concentration ranges for the isotonic agent disclosed in document D3 are within the concentration range for propylene glycol as defined in claim 1 of the patent as granted, document D3 does not link any of these concentration ranges directly to propylene glycol. In this context the Board notes that document D3 describes a wide variety of isotonic agents

as optional ingredients, including mixtures thereof, and that the specifically mentioned concentration ranges may also apply to the situation in which the composition comprises a mixture of isotonic agents. At the same time, propylene glycol is only mentioned as an example of such isotonic agents without particular distinction. The typical pharmaceutical formulations and the examples described in document D3 do not concern compositions comprising propylene glycol and thus fail to provide any further pointer towards compositions comprising propylene glycol in the concentration as defined in claim 1 of the patent as granted.

The Board therefore considers that document D3 does not directly and unambiguously disclose the compositions comprising propylene glycol in a concentration of 1-100 mg/ml as defined in claim 1 as granted.

3.3 Accordingly, the Board concludes that the patent as granted meets the requirement of novelty.

4. Inventive step

4.1 Closest prior art

The parties agreed that document D3 represents the closest prior art. The difference between the composition of claim 1 as granted and the most pertinent exemplified compositions in document D3 relied upon by the appellant-opponents as starting points in the prior art was not in dispute and concerns the presence of propylene glycol in the composition claimed in the patent instead of the isotonic agents mannitol or glycerol in the compositions described in document D3.

4.2 Formulation of the problem to be solved

4.2.1 The experimental results reported in the patent in example 1 (see paragraphs [0043] to [0054], Figures 1-4 and Table 3) and examples 2-3 (see paragraphs [0057] to [0062] and Figures 5-7) demonstrate that compositions comprising propylene glycol allow to avoid the formation of deposits on equipment and clogging of injection devices occurring with compositions comprising mannitol.

This effect from replacement of mannitol by propylene glycol was essentially not contested by the appellant-opponents. Before the withdrawal of its appeal opponent 03 had denied that the experiments in the patent with compositions having a concentration of 14 mg/ml sufficiently demonstrated the effect for the whole scope of the claim. However, the preliminary opinion expressed in the Board's communication pursuant to Article 15(1) RPBA, in which this objection was considered to lack substantiation, was not further contested.

4.2.2 The experimental results reported in the patent in example 1 (see Table 3) also demonstrate that the replacement of glycerol by propylene glycol allows for the avoidance of residual gel-like drops on the injection needle. Such gel-like drops occurred after 4 of 90 simulated injections with compositions comprising glycerol, whilst such drops did not occur with compositions comprising propylene glycol.

The appellant-opponents contested that the patent demonstrates a significant difference in frequency of the occurrence of the gel-like drops between

compositions with glycerol and compositions with propylene glycol, because the patent itself reports that glycerol did not clog the needles (see paragraph [0052]) and left no deposits on the filling equipment (see paragraph [0052]). However, the appellant-opponents have thereby not substantiated why the reported difference in the occurrence of gel-like drops on the injection needle would not be significant. The Board observes in this context that the clogging of the needle and the formation of deposits on the filling equipment concern different events with respect to the occurrence of gel-like drops. The reported absence of such clogging and formation of deposits is therefore immaterial to the significance of the reported occurrence of gel-like drops following the use of compositions comprising glycerol.

4.2.3 Example 1 of the patent involves a drop test in which droplets of the tested compositions were placed on a microscope slide and left to dry (see the patent, paragraph [0047]), a clogging test in which for a period of 9 days the same pen-system for injection was used to simulate daily injections of the tested compositions with the same needle (see the patent, paragraph [0050]) and a simulated filling test, in which the compositions were subjected to a simulated filling procedure that lasted for 24 hours (see the patent, paragraph [0053]). Examples 2 and 3 of the patent involved similar simulated filling and simulated use tests in which compositions with mannitol are directly compared with compositions with propylene glycol (see the patent, paragraphs [0057]-[0058] and [0061]).

It is not at all evident that the conditions for testing the compositions disclosed in the patent

correspond to the conditions for the practical implementation of the teaching of document D3. On the contrary, document D3 does not require or even suggest that the same needle should be used repeatedly nor that drops of the composition should be left drying or that the filling procedure should be continued uninterruptedly for 24 hours. Document D3 does, as a matter of fact, not report any formation of deposits in its experimental section, in which the stability of the filter-sterilized compositions was evaluated after the compositions were filled in glass cartridges and stored (see D3, page 36, lines 30-32).

Contrary to the arguments from the appellant-opponents the undesired phenomena observed in the patent with the use of the compositions comprising mannitol or glycerol of document D3 discussed in sections 4.2.1 and 4.2.2 above would therefore not inevitably manifest themselves upon the practical implementation of the teaching of document D3. The recognition of the relevance of these phenomena should therefore be considered to form part of the technical contribution described in the patent. A specific reference in the formulation of the objective technical problem to the avoidance of these phenomena risks to unfairly direct development towards the claimed solution, which is not permissible, as it introduces aspects of hindsight in the assessment of obviousness of the solution (see Case Law of the Boards of Appeal, *supra*, I.D.4.2.1, in particular T 800/91) .

4.2.4 The patent further reports that propylene glycol was observed to have no influence on the physical and chemical stability of liraglutide (see paragraph [0056]). According to the respondent this report is consistent with the study described in example 3 of the

patent, which did not indicate any instability of the formulations during study period of 10 days in which the formulations were stored at room temperature.

The appellant-opponents objected that the patent merely presents an allegation regarding the stability of compositions comprising propylene glycol as defined in the claims as granted. The Board observes, however, that the report in the patent on the maintained stability of the compositions comprising propylene glycol concerns a verifiable observation rather than merely some allegation.

The maintained stability of the compositions comprising propylene glycol does not imply an actual improvement with respect to the compositions comprising mannitol or glycerol as described in document D3. However, the Board finds no reason why the formulation of the objective technical problem could not refer to the purpose of maintaining the stability of the compositions.

4.2.5 In view of the advantageous effects discussed in sections 4.2.1, 4.2.2 above, which are relevant to the manufacturability and usability of the compositions and taking account of the further considerations in section 4.2.3 and 4.2.4 above the Board concludes that the problem to be solved starting from the mannitol or the glycerol based compositions of document D3 may be formulated as the provision of liraglutide containing compositions having optimized manufacturability and usability whilst maintaining stability.

4.3 Assessment of the solution

Document D3 itself provides no suggestion towards any advantage from the use of propylene glycol over mannitol or glycerol. On the contrary, document D3 recommends mannitol and glycerol as the preferred isotonic ingredients (see D3, page 19, lines 8-9).

Documents D6, D7, D47 and D48 mention the crystallisation of mannitol from highly concentrated solutions comprising 25% mannitol (see: D6, page 327, under "Incompatibilities"; D7, page 1337, under "Mannitol Crystallisation in Plastic containers"; D47, page 16, under "Warming Kettle for Storing Mannitol Injection"; D48, page 327, under "Incompatibilities"). This information does not provide any suggestion towards the improvement of the manufacturability and usability of the compositions of document D3, because the compositions in accordance with document D3 contain mannitol as an isotonic agent and thus involve far lower concentrations of mannitol than the compositions mentioned in documents D6, D7, D47 and D48. The declaration in document D49 confirms in this context that mannitol was one of the most frequently used isotonicity agents and that practical difficulties from the use of mannitol were not expected.

Documents D11, D12, D13, D16 and D18 describe the use of propylene glycol as a stabilizer in a variety of peptide containing formulations. Document D11 reports superior stabilisation of the peptide IFN-α2b from use of propylene glycol (see page 122, Table 2, entries for 1,2-propanediol). Documents D12 and D16 describe the protective effect of propylene glycol against aggregation of CNTF protein (see D12, abstract; see D16, page 22, lines 32-35). Document D13 reports that

propylene glycol raises the minimum concentration for aggregation of the LHRH peptide (see D13, page 1262, under "Conclusions"). Document D18 describes the preparation of stable formulations of highly concentrated peptides in non-aqueous solutions such as propylene glycol (see column 4, lines 53-56). However, these documents fail to provide any suggestion towards the claimed subject-matter as solution to the identified technical problem concerning the optimized manufacturability and usability. Moreover, document D11 specifically mentions that the protective effect of additives on protein formulations depends on the nature of the additive and the protein and notes that the results obtained with IFN-α2b could not be extended to LeIFN-α (see D11, page 117, right column and page 123, last sentence). Accordingly, the prior art did not present any basis for a reasonable expectation, that the advantageous stabilizing effects from propylene glycol mentioned in documents D11, D12, D13, D16 and D18 could be extrapolated to compositions comprising liraglutide, let alone for some one-way street situation regarding the replacement of mannitol or glycerol with propylene glycol.

The Handbook-excerpt of document D33 describes propylene glycol as a versatile pharmaceutical excipient in the form of a viscous liquid having a melting point of -59°C and a dynamic viscosity of 58.1 mPas at 20°C. The skilled person will further have been aware of the solid state of mannitol and the high viscosity of glycerol. However, without the benefit of hindsight the mere knowledge of the liquid state and lower viscosity of propylene glycol provided the skilled person with no suggestion that replacement of mannitol or glycerol by propylene glycol would allow

for the optimization of the manufacturability and usability of the formulations of document D3.

As solution to the identified objective technical problem the replacement of the isotonic agents mannitol and glycerol in the compositions of document D3 by propylene glycol was therefore not obvious to the skilled person.

4.4 No divergence between T 1087/15 and T 800/95

In T 1087/15 (see section 1.1.3) it was considered that knowledge of the claimed invention is indispensable in order to formulate the objective technical problem irrespective of the choice of the starting point in the prior art. The Board agrees and confirms that knowledge of the claimed invention is inevitable in order to be able to analyse it for compliance with the requirement of inventive step.

Precisely for that reason the technical problem underlying a claimed invention has to be formulated according to the established jurisprudence (see Case Law of the Boards of Appeal, *supra*, I.D.4.2.1) in such a way that it does not contain pointers to the solution or partially anticipate the solution. The assessment of the solution for obviousness in light of the prior art would otherwise be unduly influenced by an *ex post facto* view on the matter. It is in line with this jurisprudence that according to T 800/91 (see section 6, final sentence) the technical problem should not be tendentiously formulated in a way that unfairly directs development towards the claimed solution.

Accordingly, the Board does not recognize any divergence between the considerations in T 1087/15 and T 800/95

4.5 Referral G 2/21

The referral in T 116/18 pending under G 2/21 relates to the question whether post-published evidence must be disregarded if the proof of a technical effect relied upon for an inventive step rests exclusively on the post-published evidence. The Board's considerations regarding the requirement of inventive step do not rely on post-published evidence. The referral G 2/21 is therefore not considered to be of relevance to the Board's conclusions in the present case.

4.6 Accordingly, the Board concludes that the patent as granted also meets the requirement of inventive step.

Order

For these reasons it is decided that:

The appeals are dismissed

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated