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**Datasheet for the decision
of 11 May 2021**

Case Number: T 0550/18 - 3.3.04

Application Number: 05817542.3

Publication Number: 1817048

IPC: A61K38/26, A61K47/10, A61K47/26

Language of the proceedings: EN

Title of invention:
Stable formulations of insulinotropic peptides

Patent Proprietor:
NOVO NORDISK A/S

Opponent:
Sölch, Günter

Headword:
Heat treatment insulinotropic peptides/NOVO NORDISK

Relevant legal provisions:
EPC Art. 83, 123(2)
RPBA 2020 Art. 13(2)

Keyword:

Main request - Amendments - allowable (yes); Sufficiency of disclosure - (yes)

Amendment of case at the oral proceedings - taken into account (no)

Decisions cited:

T 0386/08

Catchword:



Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0550/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 11 May 2021

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
3 January 2018 concerning maintenance of the
European Patent No. 1817048 in amended form.**

Composition of the Board:

Chairman B. Claes
Members: D. Luis Alves
R. Romandini

Summary of Facts and Submissions

I. The patent proprietor (appellant) filed an appeal against the interlocutory decision of the opposition division that, account being taken of the amendments in the form of the second auxiliary request, European patent No. 1 817 048 and the invention to which it related met the requirements of the EPC. The patent is entitled "*Stable formulations of insulinotropic peptides*" and was granted for European patent application No. 05 817 542.3. It is based on an international application published as WO 2006/051110 ("application as filed").

Claims 40 to 51 of the application as filed read as follows:

"40. A method for preparation of a stable solution of a GLP-1 compound, which method comprises heating a solution of said GLP-1 compound.

41. A method according to claim 40, wherein the temperature is between 50 °C and 95 °C.

42. A method according to claim 40, wherein the temperature is between 60 °C and 95 °C.

43. A method according to claim 40, wherein the temperature is between 50 °C and 80 °C.

44. A method according to claim 40, wherein the temperature is between 70 °C and 80 °C.

45. A method according to claim 40, wherein the temperature is between 60 °C and 80 °C.

46. A method according to any one of the claims 40-45, wherein the pH is between about 8.0 to 10.5.

47. A method according to any one of the claims 40-45, wherein the pH is between about 8.0 to 10.0.

48. A method according to any one of the claims 40-45, wherein the pH is between about 7.5 to 8.5.

49. A method according to any one of the claims 40-45, wherein the pH is about 7.7.

50. A method according to any one of the claims 40-45, wherein the pH is about 8.15.

51. A method according to any one of the claims 40-50 wherein the heating is continued for a period of time which is between 3 minutes and 180 minutes."

II. The opposition proceedings were based on the grounds for opposition set out in Article 100(a) EPC, specifically lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), as well as on the grounds set out in Article 100(b) and (c) EPC. The opposition division held that the claimed subject-matter of the patent (main request) did not extend beyond the content of the application as filed (Article 100(c) EPC). However, the patent did not comply with the requirements of sufficiency of disclosure (Article 100(b) EPC). The same conclusion (insufficiency of disclosure) applied to the set of claims of auxiliary request 1 (Article 83 EPC).

III. With the statement of grounds of appeal, the appellant re-submitted the set of claims of auxiliary request 1 as the main request and submitted a set of claims of a new auxiliary request 1. They further filed a declaration by Anne-Mette Lilleøre and re-filed a declaration by Arne Staby. The appellant took the view that the ground for opposition according to Article 100(b) EPC was not sufficiently substantiated in the notice of opposition. Furthermore, they submitted arguments as to why the patent met the requirements of Article 83 EPC with the set of claims of the main request.

Claim 1 of the main request (claims 1 to 17) reads as follows:

"1. A method for preparation of a stable solution of an insulinotropic derivative of GLP-1(7-37) (SEQ ID NO. 1), which method comprises heating a solution of said insulinotropic derivative, wherein the temperature is between 50 °C and 95 °C, the pH is between 8.0 to 10.5 and the heating is continued for a period of time which is between 3 minutes and 180 minutes."

Claims 2 to 12 are dependent on claim 1. Claims 13, 14 and 16 define methods for the preparation of pharmaceutical compositions including peptides prepared by the method of claim 1, or including the method of claim 1.

Claim 15 is dependent on claim 14 and claim 17 is dependent on any of claims 1 to 16.

IV. With their reply to the appeal, the opponent (respondent) submitted arguments concerning the

requirements of Articles 83 and 123(2) EPC in relation to both the main request and auxiliary request 1. The arguments on added subject-matter were limited to claim 1 of these requests.

- V. The appellant submitted further arguments with a subsequent letter.
- VI. The board summoned the parties to oral proceedings and, in a communication pursuant to Article 15(1) RPBA, informed them of its preliminary opinion on some of the issues raised in the appeal.
- VII. The oral proceedings were held by videoconference with the agreement of both parties.

At the end of the oral proceedings, the Chair announced the board's decision.

- VIII. The appellant's arguments, where relevant to this decision, may be summarised as follows:

Main request

Amendments (Article 123(2) EPC) - claim 1

Admittance into the appeal proceedings of a line of attack presented for the first time at the oral proceedings

The respondent's attack based on the feature "*insulinotropic derivative of GLP-1(7-37)*" was submitted for the first time at the oral proceedings and should not be taken into account.

Allowability of the amendments

The application as filed disclosed that the parameter features recited in the claim were the relevant features of the method and were intended to be combined (see, e.g., page 16, lines 31 to 32, and page 17, lines 5 and 6).

The claimed method had a basis in the combination of the method disclosed in claim 40 and the ranges for temperature, pH, and time disclosed in claims 41, 46 and 51, respectively, of the application as filed.

The standard to be applied when deciding whether an amendment met the requirements of Article 123(2) EPC was direct and unambiguous derivability from the application as filed.

Sufficiency of disclosure (Article 83 EPC)

Substantiation in the notice of opposition of the ground for opposition under Article 100(b) EPC

This ground for opposition was not sufficiently substantiated in the notice of opposition. Indeed, point 7 contained a conditional objection without providing substantiation.

Admittance into the appeal proceedings of a submission presented for the first time at the oral proceedings

The respondent's argument on sufficiency of disclosure based on Figure 7 of the patent, i.e. that the patent did not show that the solutions were stable when the heating step was carried out for 3 minutes or at 50 °C, was submitted for the first time at the oral

proceedings and should not be admitted into the appeal proceedings.

Disclosure in the patent

The objections relating to the absence in the patent of a definition of a "stable solution" amounted to clarity objections.

In Figure 10 of the patent, a stability value for the reference solution was absent. Thus, it was not possible to draw a conclusion from this figure as to the relative stability of the treated solution at 50 °C versus the reference solution. As regards the effect of the heat treatment on stability, the skilled person would instead rely on the results shown in the figures which did include a reference value.

Figures 2 and 4 of the patent related to treatment at 60 °C and 80 °C, respectively. Therefore, they could not demonstrate that no stability increase was present at 50 °C. Moreover, Figure 2 showed an increase in stability with treatment at pH 10, for 20 minutes, when the comparison was with the correct reference, i.e. with the reference at pH 10.

As regards stability at the lower end of the heating time range, Figure 7 showed an improvement in stability when the heating was carried out for 5 minutes, as well as for 1 minute. Based on these results, an improvement would also be expected at an intermediate point, i.e. when the heating was carried out for a period of 3 minutes. This figure related to heat treatment at 50 °C.

As regards stability at the lower end of the heating temperature range, on the basis of the results depicted in Figure 6 for 40 °C and 60 °C, the skilled person would have expected improved stability when heating was carried out at 50 °C. Therefore, it could not be concluded from the results shown in the patent that there was no effect on the stability of the solution when heating was carried out at 50 °C.

The opponent had not put forward any serious doubts. They provided no evidence that the solutions were not stable when the treatment temperature was 50 °C or when the period of time was 3 minutes.

IX. The respondent's arguments, where relevant to this decision, may be summarised as follows:

Main request

Amendments (Article 123(2) EPC) - claim 1

Admittance into the appeal proceedings of a line of attack presented for the first time at the oral proceedings

The feature "*insulinotropic derivative of GLP-1(7-37)*" was disclosed only in a list of three alternatives on page 8, lines 28 and 29, of the description. Selecting one of the alternatives in the claim resulted in added subject-matter.

This line of argument was part of the appeal proceedings because the decision under appeal mentioned the passage on page 8 of the description where the feature was mentioned.

Allowability of the amendments

While the application as filed did disclose the individual features in the claim, it did not disclose the combination thereof.

Claim 40 of the application as filed did not disclose that the temperature, pH and period of time were the crucial parameters of the method. Claims 46 and 51 of the application as filed each comprised multiple embodiments because they referred back to multiple claims. Claim 51 referred back to multiple claims in addition to claim 46, comprising a total of eleven embodiments, while claim 46 in turn referred back to multiple claims in addition to claim 41, comprising a total of six embodiments. None of claims 40, 41, 46 and 51 nor the description (see page 15, line 27, to page 16, line 26) of the application as filed referred to the combination of ranges now recited in the claim as being preferred. Therefore, the ranges of the features now recited in the claim resulted from a combination from two lists.

Sufficiency of disclosure (Article 83 EPC)

Substantiation in the notice of opposition of the ground for opposition under Article 100(b) EPC

In section 5.2 of the notice of opposition, it was argued that the examples of the patent could not be reproduced, and in section 7, sufficiency of disclosure was addressed.

Admittance into the appeal proceedings of a submission presented for the first time at the oral proceedings

No arguments were submitted in this regard.

Disclosure in the patent

Claim 1 required that the method resulted in a stable solution. However, the patent provided neither a definition of a "stable solution" nor the absolute value which was indicative of a stable solution according to the fluorescence assay used in the patent to determine stability.

Figure 2 showed that, at pH 8, the stability of the liraglutide solution after heating for 1 minute, as well as for 20 minutes, was similar for the reference and the treated sample. The same applied when comparing the results shown for composition P004 in Figure 10 with those shown in Figure 2. Additionally, the value shown in Figure 2 for heating at pH 10, for 20 minutes, was lower than the reference value. This was in contradiction with the teaching that the heat treatment according to the claim resulted in a stable solution, in contrast to a non-treated solution.

No error bars were shown in the figures, and therefore the differences were considered to be not statistically significant.

Only Figures 7 and 10 showed values for treatment at 50 °C. From Figure 7 it could be derived that stability improved when heating was carried out at a higher temperature or for a longer time. However, sufficiency of disclosure required that it was plausibly shown that stability could be achieved also at the lower limits of

the range for each parameter, i.e. here at 3 minutes and at 50 °C. However, the patent provided no evidence of this. Figure 10 did not show values for reference samples. Additionally, Figure 10 showed lower stability as a result of treatment at 50 °C when compared to treatment at 60 °C.

- X. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request, or, alternatively, on the basis of the set of claims of auxiliary request 1, both of which were filed with the statement of grounds of appeal, and that the case not be remitted to the opposition division for further prosecution.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Main request

Amendments (Article 123(2) EPC) - claim 1

Admittance into the appeal proceedings of a line of attack presented for the first time at the oral proceedings

2. At the oral proceedings, the respondent submitted for the first time an attack based on the feature "*insulinotropic derivative of GLP-1(7-37)*". They argued that the feature was disclosed only in a list of three alternatives on page 8, lines 28 and 29, of the

application as filed. By selecting only one of the alternatives in the claim, its subject-matter was defined by a combination of features which was not disclosed in the application as filed.

3. Since this attack was advanced for the first time at the oral proceedings, it constitutes an amendment to the respondent's case, as referred to in Article 13(2) RPBA 2020. As a consequence, it shall be taken into account only in exceptional circumstances, which need to be justified with cogent reasons.
4. In this respect, the respondent has only submitted that the above-mentioned passage on page 8 of the description was mentioned in the decision under appeal; in their view, it was part of the appeal proceedings for this reason.
5. The board understands the respondent's argument to be that the attack presented at the oral proceedings did not constitute a change of their case. However, the opposition division referred to this passage not in order to deal with the point made by the respondent in the appeal proceedings. Rather, the opposition division referred to that passage to indicate a basis in the application as filed for the feature "*GLP-1(7-37), insulinotropic analogue thereof and insulinotropic derivatives thereof*", in the context of the main request pending at that time (see point 1.3 of the decision under appeal). Since this feature recited all three alternatives found in the passage on page 8 of the description, the issue of selecting one item from a list of three alternatives did not arise in the opposition proceedings. Accordingly, it was not part of the decision under appeal.

Thus, the respondent's submission does not convince the board that the attack at hand does not constitute an amendment to the respondent's case.

6. Furthermore, the respondent has not presented cogent reasons that could convince the board of the presence of exceptional circumstances. Accordingly, the board has decided not to take into account the attack based on page 8 of the application as filed.

Allowability of the amendments

7. The claimed method comprises a heating step characterised by three parameters: temperature, pH and a period of time (see section III.).
8. On page 15, line 27, to page 16, line 26, the application as filed discloses ranges of values for the parameters characterising the heating step in the method. Although the specific combination of ranges for the parameters defining the heating step in the claimed method is not disclosed, each combination disclosed in this passage relates to the temperature, pH and period of time. Thus, this passage consistently discloses no other than the same three parameters as recited in claim 1 of the main request. Claims 40 to 51 as filed (see section I.) also disclose only the three parameters mentioned above. Accordingly, the board sees no merit in the respondent's argument that the application as filed did not disclose these three parameters in combination.
9. The above-mentioned passages of the application as filed disclose multiple ranges of values for each of these parameters. It cannot be considered that each and every combination of value ranges for each of

temperature, pH and period of time is disclosed. Nevertheless, in the board's view, the skilled person would directly and unambiguously derive the specific combination of those ranges that are the broadest for each of the parameters. In the present case, this is the combination of the ranges 50 to 95 °C, pH 8.0 to 10.5, and 3 minutes to 180 minutes, i.e. the ranges in the claim.

10. The respondent argued that neither the claims as filed nor the passage of the description on page 15, line 27, to page 16, line 26, disclosed a preference for the ranges now recited in the claim. However, under the circumstances of the case, the board is of the view that it is not necessary that these ranges are disclosed as being "preferred" because, as reasoned above, the board considers the combination of the most general ranges disclosed for each of the parameters to be directly and unambiguously derivable by the skilled person.
11. Thus, the application as filed discloses the subject-matter of claim 1 (Article 123(2) EPC).

Sufficiency of disclosure (Article 83 EPC)

Substantiation in the notice of opposition of the ground of opposition under Article 100(b) EPC

12. The appellant did not call into question the admissibility of the opposition. Indeed, at least one ground for opposition was considered to be substantiated. The appellant challenged the opposition division's decision to hold substantiated the ground of opposition under Article 100(b) EPC.

13. In view of the board's finding that the patent sufficiently discloses the invention as defined in the claims of the main request (see points 17. to 37. below), the board does not need to make a decision on this point, since it would not change the outcome of the appeal proceedings.

Admittance into the appeal proceedings of a submission presented for the first time at the oral proceedings

14. At the oral proceedings, the respondent argued that the patent did not sufficiently disclose the invention over the whole range claimed, as the patent did not show that a stable solution could be obtained when carrying out the method at the lower limits of the ranges for temperature and duration of heating, i.e. at 50 °C for 3 minutes.
15. The appellant objected that this submission had been presented for the first time at the oral proceedings before the board.
16. Whether this submission is to be taken into account or not need not be decided since it would not change the outcome of the appeal proceedings. Indeed, when considering it on the merits, the board has come to the conclusion that the requirements of Article 83 EPC are met (see points 17. to 37. below).

Disclosure in the patent

17. The following experimental results disclosed in the patent are pertinent for the decision:
- 17.1 Figure 2 of the patent shows results of stability assays after heating at 60 °C, at pH 8 and pH 10, at

varying durations of heating. At pH 8, there is a trend of stability increase with an increased duration of heating; this trend being very marked at pH 10.

- 17.2 Figure 4 shows corresponding results after heating at 80 °C. For both pH values, there is a clear trend of stability increase with an increased duration of heating.
- 17.3 Figure 6 shows stability results at varying temperatures at pH 10 after 15 minutes of heating. The results show a trend of stability increase with an increasing temperature (from 22 °C to 40 °C, 60 °C and 80 °C).
- 17.4 Figure 7 shows stability results at pH 10, at 50 °C and 80 °C, with varying durations of heating. For both temperatures, there is a trend of increased stability with an increased duration of heating; the trend being very marked at 80 °C.
- 17.5 Figure 10 shows the results when the heat treatment lasted 60, 90 or 120 minutes, and was carried out at 50, 60 or 70 °C. Two solutions were tested, designated P004 and P019. The reference value, i.e. stability in the absence of a heat treatment, is not depicted. From a comparison of the results for solution P004, at the lowest temperature tested, i.e. 50 °C, a trend in increased stability with duration of the treatment is not recognisable for the tested 60 to 120 minutes. The same applies for solution P019, with the same tested durations of the treatment. When comparing each solution at different temperatures at the same duration of heating, a trend of increased stability with increased temperatures is recognisable.

18. The opposition division based its finding that the patent in the form as now considered by the board (see sections II. and III.) did not sufficiently disclose the claimed invention on the experimental results presented in Figure 10 of the patent (pertaining to Example 14). They held that the results demonstrated that, at pH 8.0, for the P004 batch of the liraglutide solution, heating the solution at 50 °C provided "*poor stability results*" at each indicated period of heating (60, 90 and 120 minutes), whereas heating at 60 °C provided intermediate results, and heating at 70 °C much better values. Thus, Figure 10 represented a verifiable fact that at temperatures around 50 °C the skilled person would not reliably obtain a stable solution with the claimed method and, hence, serious doubts would be raised that the claimed invention could be carried out by the skilled person, without undue experimentation or inventive skill, by simply following the guidance provided in the patent.
19. Figure 10 does not, however, include data on the reference value of untreated sample solutions, i.e. a value in the absence of a heat treatment. The board cannot therefore derive from the disclosure in Figure 10 a basis for concluding that at 50 °C no increased stability can be achieved with the claimed method.
20. In fact, only Figures 6 and 7 show results at 50 °C or lower, and include a reference value, i.e. a value in the absence of heat treatment. Figure 7 shows an improvement at 50 °C versus the reference, for treatment for 1 minute as well as for 5 minutes. Figure 6 does not depict results of treatment at 50 °C but nevertheless provides information in this regard since it shows a reference value, i.e. for a solution

at 22 °C, and values for treatment at 40 °C, 60 °C and 80 °C. It shows an increase in stability already at 40 °C.

21. Therefore, the board cannot derive from the patent any evidence that there is no increase in stability over the reference value with heat treatment at 50 °C.
22. All the arguments brought forward by the respondent in the appeal rely solely on an analysis of the experimental results in the patent; no other evidence having been filed. However, in accordance with established case law of the boards of appeal, a finding of lack of sufficiency of disclosure presupposes serious doubts substantiated by verifiable facts (see decisions cited in the Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, II.C.5.3., last paragraph, and II.C.9).
23. The respondent referred to the experimental results depicted in Figure 2 of the patent in support of their line of argument that the patent did not demonstrate that a stable solution was obtained at the lower values of the range for temperature and duration of the heating. The results obtained at 1 minute and at 20 minutes were very similar to those for the reference. In the absence of error bars, any difference in stability would not be statistically significant.
24. The argument therefore is not that Figure 2 shows that there is no increase in stability over the reference in the conditions in the experiment, i.e. at 60 °C. Rather, it is that the patent does not show a stability increase which is statistically significant.

25. In a related line of argument, at the oral proceedings the respondent further argued (see section IX. and point 14.) that Figure 7 of the patent does not demonstrate an increase in stability when the parameters temperature and duration of the heating have the values 50 °C and 3 minutes, respectively. Also in this regard, the respondent submitted that the absence of information on the statistical significance of any differences between the different heating conditions meant that the patent does not show an improvement with the claimed heating treatment.
26. However, in the board's view this is not a reason for concluding that the patent does not sufficiently disclose the claimed invention. Indeed, there is no requirement for a patent to demonstrate that every embodiment encompassed by the claims can be obtained (see also decision T 386/08, points 56 and 67 of the Reasons). Thus, both lines of argument above, relying on Figure 2 and Figure 7, respectively, fail for this reason.
27. The respondent further contended that the value shown in Figure 2 for treatment for 20 minutes at pH 10 was lower than that for the reference sample. However, the appropriate comparison is with the reference solution at the same pH, i.e. pH 10. When compared in this way, the measured value indeed increases with the duration of the heating treatment and this increase is already shown to be present when heating for 1 minute.
28. The respondent has also argued that a comparison of the results in Figures 2 and 10 of the patent showed that heat treatment at 50 °C did not have an effect on stability (comparison of the value for solution P004,

in Figure 10, with that for the reference, in Figure 2).

29. This comparison presupposes that the two figures refer to the same solution, i.e. P004. However, the board has not been provided with any evidence to this effect. Therefore, the implication that the results in Figure 10 are to be compared with the reference in Figure 2 must fail.
30. It was additionally argued that Figure 10 shows poorer stability for solutions treated at 50 °C as compared to solutions treated at 60 °C.
31. However, a reference value for the untreated sample is absent from this figure. Therefore, the only conclusion that may be drawn from this figure is that an increase in temperature results in an increase in stability and not that carrying out the method at 50 °C does not lead to a stability increase.
32. The respondent also argued that the patent lacked a clear definition of a "stable solution" and lacked an absolute value indicative of a stable solution when measuring stability according to the methods disclosed in the patent.
33. In the board's view, these arguments concern the clarity of the claims pursuant to Article 84 EPC and not the sufficiency of the disclosure under Article 83 EPC.
34. According to the case law of the boards of appeal of the EPO, if an argument is made that insufficiency of disclosure arises from a lack of clarity, it is not sufficient to establish a lack of clarity of the claims

in order to establish insufficiency of disclosure. Rather, it is necessary to show that the patent as a whole does not enable the skilled person, relying on the description and on their common general knowledge, to carry out the invention (see Case Law of the Boards of Appeal of the EPO, 9th edition, 2019, II.C.8.2.).

35. The board agrees with this case law. In the present case, there is no evidence that the solutions of GLP-1(7-37) derivatives obtained by the methods disclosed in the patent were not stable according to the definitions given in paragraphs [0010] and [0011] of the patent.

36. Finally, the respondent submitted that the patent lacked disclosure of the conditions essential for reproducing the examples such as the identification of any additional components present in the tested solutions as well as the concentration thereof and the concentration of the insulinotropic compounds. However, the respondent has in this context provided no reasons as to why different concentrations or different additional components would affect the results shown in the patent. The board has thus no reason to assume that, depending on the additional components present, the heat treatment might lead to a decrease or no increase in stability of the insulinotropic compound. The same is true of the concentration of the components. This line of argument cannot therefore substantiate serious doubts either.

37. Thus, in view of the above considerations, the requirements of Article 83 EPC are met.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the opposition division with the order to maintain the patent with the set of claims of the main request filed with the statement of grounds of appeal and a description and figures to be adapted thereto.

The Registrar:

The Chair:



I. Aperribay

B. Claes

Decision electronically authenticated