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Datasheet for the decision of 10 October 2007

Case Number: T 0025/06 - 3.3.04

Application Number: 99945649.4

Publication Number: 1112082

IPC: A61K 38/16

Language of the proceedings: EN

Title of invention:
Stable liquid formulations of botulinum toxin

Patentee:
Solstice Neurosciences, Inc.

Opponents:
Société de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.)
ALLERGAN

Headword:
Botulinum toxin/SOLSTICE NEUROSCIENCES

Relevant legal provisions:
EPC Art. 123(2)(3), 84, 111(1)
EPC R. 57a

Keyword:
"Main request: Added subject-matter (no); Broadening of the scope of protection (no); Clarity and support in the description (yes); Amendments occasioned by the grounds of opposition (yes); Remittal (yes)"

Decisions cited:
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Catchword:
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Case Number: T 0025/06 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 10 October 2007

Appellant: (Patent Proprietor)
Solstice Neurosciences, Inc.
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Representative:
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 22 November 2005 revoking European patent No. 1112082 pursuant to Article 102(1) EPC.

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
R. Moufang

Summary of Facts and Submissions

I. European Patent No. 1 112 082 based on application No. 99 945 649.4 (published as WO 00/15245) and having the title "Stable liquid formulations of botulinum toxin" was granted on the basis of 23 claims, of which claim 1 read as follows:

"1. A stable liquid pharmaceutical botulinum toxin formulation, comprising a pharmaceutically acceptable buffer capable of providing a buffered pH range between about pH 5 and pH 6, and isolated botulinum toxin; wherein said formulation is stable as a liquid for at least one year at a temperature between about 0 and 10°C, or at least 6 months at a temperature between about 10 and 30°C."

II. Notices of opposition were filed by opponents O1 and O2 requesting the revocation of the European patent on the grounds of lack of novelty, lack of inventive step and insufficiency of disclosure (Article 100(a) and (b) EPC).

III. The opposition division only dealt with the formal admissibility under Articles 123 and 84 EPC of the claims of the Main Request and of the 1st to 7th Auxiliary Requests then before it, which was denied on the grounds that claim 1 of all these requests included the expression "buffered saline" which was said to be unclear and not originally disclosed. Hence the patent was revoked.

IV. The appellant (patentee) filed an appeal against the decision of the opposition division. The grounds of appeal included a Main Request and an Auxiliary Request I. Claims 1 and 11 of the Main Request read as follows:

"1. A stable, ready-to-use liquid pharmaceutical formulation comprising serum albumin; a pharmaceutically acceptable buffered saline which provides a buffered pH range between pH 5 and pH 6; and isolated botulinum toxin that is stable in said formulation for at least one year at a temperature between about 0 and 10°C, or for at least 6 months at a temperature between about 10 and 30°C."

"11. The formulation of claim 10, wherein the stable, ready-to-use liquid pharmaceutical formulation comprises 100 mM sodium chloride; 10 mM succinate buffer at a buffered pH of 5.6; 0.5 mg/mL human serum albumin; and botulinum type B present at a concentration of 5,000 ± 1000 U/ml."

Claims 2 to 10 related to specific embodiments of the formulation according to claim 1. Claims 12 to 22 were directed to medical uses of the formulation of claim 1 in Swiss type claim format.

V. The following documents are cited in the present decision:

D1 Goodnough M.C. et al., Applied and Environmental Microbiology, Vol. 58, No. 10, pages 3426-3428 (1992);

D12 US-A-5,714,468;

D17 McLellan, K. et al., Toxicon, Vol. 34, No. 9, pages 975-985 (1996);

D19 Schantz E.J. and Johnson E.A. in Therapy with Botulinum Toxin, edited by Joseph Jankovic and Mark Hallett, Marcel Dekker, New York, Basel, Hong Kong, pages 41-49 (1994);

D24 Asher B., J. Méd. Esth. et Chir. Derm., Vol. XXIII, pages 159-166 (1996);

D33 Schantz E.J. et al., Journal of the AOAC, Vol. 61, No. 1, pages 96-99 (1978).

VI. The appellant's arguments in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

Main request
Rule 57a EPC

– The amendments had been occasioned by the grounds of opposition specified in Article 100 EPC.

Article 123(2)(3) EPC
"Buffered saline"

– Support for the term "buffered saline which provides a buffered pH range between pH 5 and pH 6" could be found on page 7, lines 3 to 7 of the published WO application in combination with Example 1 on pages 19 ff. and the statement on

page 28, lines 24 and 25, of the published WO application.

– There was a basis for the expression "buffered saline" in claim 1 on the grounds that (i) the "buffered saline" was a component of the liquid pharmaceutical formulation as claimed; (ii) the term "buffer" also related to a salt solution; (iii) a saline alone, while providing the required osmotic value, would not achieve any buffering capacity; and (iv) the term "buffered saline" was synonymous with "physiological sodium chloride solution".

"Stability requirement"

– According to page 6, lines 1 to 3 of the published WO application, "stable" related to the retention of biological activity or potency by the botulinum toxin.

Article 84 EPC
"Buffered saline"

– The skilled person would understand that the term "saline" could only mean "physiological sodium chloride solution".

"Ready-to-use"

– The term "ready-to-use" meant that the liquid pharmaceutical formulation could be used as needed by the clinician, without further reconstitution.

This interpretation was in line with the remaining disclosure in the patent in suit.

VII. After having raised objections, inter alia, under Rule 57a, Articles 84 and 123(2)(3) EPC against the claims of the Main request (see the "reasons" for more details), the respondents (opponents O1 and O2) withdrew their oppositions with letters dated 8 October 2007 and 18 May 2007, respectively.

VIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of claims 1 to 22 of the Main request filed with the grounds of appeal dated 3 April 2006, with the proviso that claim 11 is made dependent not from claim 10 but from claim 1.

Reasons for the Decision

Main request

1. At the appeal stage up to the withdrawal of their oppositions, the respondents (opponents O1 and O2) raised objections, inter alia, under Rule 57a, Articles 84 and 123(2)(3) EPC against the claims of this request. The board will consider in the following whether or not any of these objections were justified.

Rule 57a EPC

2. The respondents objected to the introduction of dependent claim 11 as being not occasioned by any ground of opposition.

Following the change in claim dependency requested by the appellant (see paragraph VIII supra), claim 11 relates to a specific embodiment of the composition according to claim 1, wherein the parameters correspond to those of the composition of Example 1B of the patent in suit. Claim 11 thus serves to further adequately interpret claim 1 and may be considered as being occasioned by the grounds of oppositions, i.e., the potentially novelty-destroying prior art documents D1, D12 to D19, D24 and D33. Therefore, the board concludes the requirements of Rule 57a EPC are met.

Article 123(2)(3) EPC
"Buffered saline"

3. In the respondents' opinion, there was no basis for the expression "buffered saline" in claim 1 on the grounds that (i) the buffered saline was not part of the formulation, but only something in which the formulation could be stored (see page 7, first full paragraph of the published WO application); (ii) the term "buffer" related to the salt, not to the solution of a salt; (iii) since "buffer" and "saline" were separate entities, the term "buffered saline" could be interpreted as a saline devoid of buffer; and (iv) "buffered saline" was not synonymous with "physiological buffer" but rather alternative thereto.

4. As regards ground (i) above (the buffered saline was not part of the formulation), it is stated on page 7, first full paragraph of the published WO application, that the "liquid pharmaceutical formulation" can be stored in a "buffered saline". Therefore, in the

board's judgement, once said "liquid pharmaceutical formulation" is stored in a "buffered saline", the latter becomes a component of the liquid pharmaceutical formulation as claimed, as illustrated by Table 1 of Example 1 (see ibidem, page 19), describing the preparation of a ready-to-use stable botulinum toxin formulation wherein the buffered saline (10 mM succinate + 100 mM sodium chloride) is part of the formulation. Hence, there is a basis in the published WO application for a "liquid pharmaceutical formulation comprising a buffered saline".

5. As for ground (ii) above (the term "buffer" related to the salt, not to the solution of a salt), the term "buffer" relates both to the salt (see page 13, lines 14-16 of the published WO application: "succinate, phosphate, acetate, citrate, aconitate, malate and carbonate") prior to its dissolution **and** the solution comprising said salt (see ibidem, page 7, lines 8-9: "a salt, which, when dissolved in an aqueous medium"). Moreover, it is only in solution that a salt can exert its buffering capacities (transfer of hydrogen ions). Therefore, the term "buffer" within the context of the published WO application also relates to a salt solution.

6. As for ground (iii) above ("buffered saline" could be interpreted a saline devoid of buffer, since "buffer" and "saline" were separate entities), the board is unable to find a basis in the published WO application for interpreting the term "buffered saline" as a saline devoid of buffer. This interpretation also does not make technical sense because, while a saline alone would provide a particular osmotic value, it would not

achieve the buffering capacity required by present claim 1.

7. As regards ground (iv) above ("buffered saline" was not synonymous with "physiological buffer" but rather alternative thereto), the board views a "buffered saline" as a particular kind of "physiological buffer". The latter term is defined on page 7, lines 13 to 15, of the published WO application as a buffer that is non-toxic when administered as part of a pharmaceutical preparation. A prerequisite for a physiological buffer to be non-toxic is that it must be isotonic with blood. To this effect, the desired osmolarity is achieved by the presence of a given amount of saline. This view is supported by Example 1A describing a 0.85% w/v buffered saline ([2.7 + 5.8]mg/ml = 8.5 mg/ml = 0.85 g/100 ml = 0.85 g/100 g), in keeping with the 0.85% w/v NaCl normally added to get a physiological solution (see e.g. document D17, page 977 under "Bioassay for botulinum toxin type A", last sentence).

"Stability requirement"

8. The respondents raised an objection that new matter had been added by changing the stability requirement in present claim 1 from "wherein said formulation is stable" (granted claim 1) to "botulinum toxin that is stable in said formulation". However, according to page 6, lines 1 to 3 of the published WO application, "stable" refers to the retention of biological activity or potency by the botulinum toxin. Moreover, Example 2 of the published WO application describes assays to determine the stability by measuring the potency of the botulinum toxin in the claimed liquid formulations.

Therefore, the wording "botulinum toxin that is stable in said formulation" in present claim 1 has a basis in the application as filed.

9. The respondents also considered the above amendment as violating Article 123(3) EPC, arguing that present claim 1 covered formulation not covered by granted claim 1, wherein the instability in the formulation was not caused by the toxin itself.

It follows from the above board's conclusion in relation to Article 123(2) EPC that granted claim 1 cannot cover formulations where the instability is not caused by the botulinum toxin itself. Therefore, no problem under Article 123(3) EPC arises, either, since claim 1 of the Main Request does not cover formulations that were not covered by the granted claims.

10. In conclusion, the claims satisfy the requirements of Article 123(2)(3) EPC.

Article 84 EPC
"Buffered saline"

11. The respondents argued that this term was not synonymous with "physiological sodium chloride solution" but could also refer to any salt solution, such as e.g. a magnesium sulfate containing solution.

However, in the board's judgement, the skilled person would understand that the term "saline" can only mean "physiological sodium chloride solution" in the sense of Example 1A of the patent describing a 0.85% w/v buffered saline and of the 0.85% w/v NaCl physiological

solution referred to in e.g. document D17, page 977 under "Bioassay for botulinum toxin type A", last sentence (see point 7 supra). This is because the limitation introduced by the phrase "pharmaceutically acceptable" in present claim 1 precludes salts that are not isotonic (causing a possible haemolysis), or that may be toxic upon administration, such as magnesium sulfate.

"Ready-to-use"

12. The respondents maintained that the term "ready-to-use" lacked clarity. If the above expression meant that the liquid formulation could be used immediately on a patient, in the respondents' view, this interpretation was contradicted by paragraph [0022] of the patent, stating that the formulation could be a concentrated formulation to be diluted in a similar or different liquid prior to use.

Paragraph [0005] of the patent in suit discusses the disadvantages of the prior art botulinum toxin formulations, inter alia, the fact that a physician wishing to administer botulinum toxin had to reconstitute it immediately prior to use (see also page 4, lines 6 to 9 of the specification).

The term "ready-to-use" turns up for the first time in paragraph [0006] of the specification and provides the definition of the expression "ready-to-use liquid pharmaceutical formulation" as being a formulation that can be used as needed by the clinician, without further reconstitution. This interpretation is line with the remaining disclosure in the patent in suit (see for

example, paragraph [0040], line 9: "without further re-constitution by the physician"). Therefore, the term "ready-to-use" is not obscure to the skilled person.

13. The respondents argued that paragraph [0022] of the patent ("concentrated formulation which is diluted") contradicted the definition of the term "ready-to-use" as meaning "liquid formulation that can be could be used immediately on a patient".

However, although according to the above embodiment of paragraph [0022] of the patent the claimed liquid formulation may comprise concentrated amounts of toxin that need to be diluted by the physician for convenience, these concentrated formulations themselves do not need to be reconstituted by the physician from lyophilized toxin before administration to a patient (rather than being susceptible of "immediate use on a patient", as argued by the respondents). Therefore, the board does not see the contradiction pointed out by the respondents.

14. In view of the foregoing, the claims of the Main request fulfil the requirements of Article 84 EPC.

Remittal

15. In the decision under appeal, the opposition division only dealt with the formal admissibility under Articles 123 and 84 EPC of claims different from the claims presently on file. For the purpose of the present decision the board has already examined the claims of the new Main Request as to whether or not they fulfil the requirements of Rule 57a and

Articles 123(2)(3) and 84 EPC (see points 2 to 14 supra), but, in order not to deprive the appellant of the possibility to have his invention examined by two instances, and in accordance with the established jurisprudence of the boards of appeal, the board uses its discretion under Article 111(1), second sentence, EPC, and remits the case to the first instance for further prosecution to consider the remaining issues.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution on the basis of claims 1 to 22 of the Main request filed with the grounds of appeal dated 3 April 2006, with the proviso that claim 11 is made dependent not from claim 10 but from claim 1.

The Registrar: The Chair:

P. Cremona U. Kinkeldey