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**Datasheet for the decision
of 2 May 2022**

Case Number: T 0240/20 - 3.3.08

Application Number: 11789976.5

Publication Number: 2578228

IPC: C12N9/52, G01N30/96, A61K38/00

Language of the proceedings: EN

Title of invention:
NON-DIFFUSIVE BOTULINUM TOXIN CAUSING LOCAL MUSCLE PARALYSIS,
AND PURIFICATION METHOD THEREOF

Patent Proprietor:
Medexgen Inc.

Opponent:
Wächtershäuser & Hartz
Patentanwaltpartnerschaft mbB

Headword:
Non-spreading botulinum toxin and purification method thereof/
MEDEXGEN

Relevant legal provisions:
EPC Art. 56

Keyword:

Main request and auxiliary requests 2 to 3 - inventive step
(no)

Decisions cited:

Catchword:



Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0240/20 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 2 May 2022

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Decision under appeal:

**Interlocutory decision of the Opposition
Division of the European Patent Office posted on
10 December 2019 concerning maintenance of the
European Patent No. 2578228 in amended form.**

Composition of the Board:

Chairman B. Stolz
Members: D. Pilat
 A. Bacchin

Summary of Facts and Submissions

- I. European patent No. 2 578 228 is based on European patent application No. 11789976.5 (published as WO2011/152618 on the 8 December 2011). The patent was opposed on the grounds of Article 100(a) in conjunction with Article 56 EPC, and of Articles 100(b) and (c) EPC. An opposition division considered that the main request extended beyond the content of the application as filed under Article 100(c) EPC and took the view that auxiliary request 1 and the description adapted thereto complied with the requirements of the EPC.
- II. Opponent (appellant) lodged an appeal against the decision of the opposition division.
- III. The respondent (patent proprietor) did not reply in substance to the statement of grounds of appeal.
- IV. Oral proceedings were requested as an auxiliary measure by both parties and the parties were summoned accordingly. Respondent withdrew its request with a letter dated 3 December 2021 and announced its non-attendance at the scheduled oral proceedings.
- V. In a communication sent in preparation of the oral proceedings, the board provided observations on procedural issues and expressed a provisional opinion on some issues concerning Articles 123(3), 84, 83 and 56 EPC.
- VI. Appellant withdrew its request for oral proceedings with a letter dated 23 December 2021. Oral proceedings were cancelled.

VII. None of the parties replied in substance to the board's communication.

VIII. Independent claims 1 to 3 of the main request read as follows:

"1. A method for purifying a non-spreading botulinum toxin, comprising the steps of: separating the botulinum toxin type A product into subfractions by conducting ion-exchange chromatography using pH 4.5-5.5 buffer and 0.02-0.2 M of sodium chloride (NaCl); and collecting a non-spreading botulinum toxin subfraction, which has an A260/A280 value of 0.4-0.6, from the said separated subfractions.

2. A non-spreading botulinum toxin preparation, which is purified by the above method comprises, Zn, Fe and Mg ion concentrations at least 150, 80, and 140 ppb per 100 U/ml, respectively."

3. A method for determining a non-spreading botulinum toxin, comprising injection the non-spreading botulinum toxin preparation of claim 2 into the either left or right hind limb calf muscle of mouse (4-6 wk old, weighing 18-22g) in an amount equivalent to 1.5-3 times the LD₅₀ of the toxin; and determining whether the hind limb muscles injected and respiratory muscles of the mouse were paralyzed and whether the mouse died."

Dependent claim 4 defines a specific embodiment of the method of claim 3.

IX. The following documents are referred to in this decision:

D8: "Ion Exchange Chromatography & Chromatofocusing - Principles and Methods; Amersham Biosciences 11-0004-21; pages 1 to 185;

D23: Tse CK, et al. "Preparation and Characterisation of Homogeneous Neurotoxin Type A from Clostridium botulinum." Eur. J. Biochem., 1 March 1982, vol. 122(3), pages 493 to 500, (1982).

X. The submissions made by the appellant, insofar as relevant to the present decision, are summarized as follows:

Main request (Auxiliary request 1 as maintained by the opposition division).

Inventive step (Article 56 EPC)

Document D23 represented the closest prior art with regard to the method of claim 1 and with regard to the non-spreading botulinum toxin of claim 2.

Document D23 related to the preparation and characterization of homogeneous neurotoxin type A from Clostridium botulinum. It described the isolation of Haemagglutinin-Neurotoxin complexes from culture medium by acid precipitation, clarified by centrifugation, re-extracted with buffer, pooled and subjected to ribonuclease treatment (see page 494, left column, 3rd and 4th paragraphs). The purification procedure was summarized in Table 1. A clear solution was subjected to ion-exchange chromatography on a DEAE-Sephacel column, equilibrated in a 0.05 M sodium citrate buffer at pH 5.5. The botulinum toxin was obtained in the void volume, and fractions having a 260/280 nm absorbance ratio of 0.54-0.58 were pooled.

The difference between the purification method of document D23 and of claim 1 was that the method of document D23 used a 0.05 M sodium citrate buffer, pH 5.5, whereas the method of claim 1 required the use of a buffer comprising 0.02-0.2 M of sodium chloride (NaCl).

The "non-spreading" effect was unclear. Did the method of claim 1 aim at further purifying a botulinum toxin that is already "non-spreading" or did it aim at separating a "non-spreading" botulinum toxin from a mixture of both "spreading" and "non-spreading" botulinum toxin? Was the botulinum toxin of claim 2 "non-spreading" by itself or was it the ingredients of the preparation that rendered it "non-spreading"?

The effect underlying the use of a different buffer in the method of claim 1 was unknown. The "non-spreading" effect of the botulinum toxin in claims 1 and 2 had no clear definition in the art. Hence, it could not be considered as a distinguishing feature over the prior art.

The difference between document D23 and the preparation of claim 2 was that it explicitly comprised Zn, Fe and Mg ion concentrations.

However, it was unclear whether the "non-spreading" botulinum toxin preparation was non-spreading in itself or whether the components present in the preparation caused this property. It was further unclear whether the "non-spreading" botulinum toxin according to claim 2 purified by the method of the patent or by the method of document D23 were at all distinguishable.

Given that the "subfraction pII obtained in Example 1" and the "commercial product" defined as Allergan's Botox were prepared according to an unknown purification method, the preparations obtained thereby most certainly differed by more than only the Zn, Fe and Mg ion concentrations.

It was unclear whether the "non-spreading" effect of the toxin in the preparation could be assigned only to the Zn, Fe and Mg ion concentrations.

Since neither the differences between the method of document D23 and the method of claim 1 nor the differences between the "commercial product" and the preparation of claim 2, were shown to result in a technical effect, the objective technical problem solved had to be formulated as the provision of an alternative process for purifying a botulinum toxin and as the provision of an alternative botulinum toxin preparation, respectively.

The technical problem of providing a product with an improved therapeutic range was not based on any evidence and comparison between the product disclosed in document D23 and claim 2. This technical problem was accordingly not solved.

The skilled person, faced with the technical problem of providing an alternative purification method to the one disclosed in document D23, would have turned to document D8, which mentioned that "[T]he counter-ions (salt ions) used in IEX are almost always Na⁺ for cation exchange and Cl⁻ for anion exchange. Salts such as NaCl have a chaotropic character (i.e. an ability to make water less polar) and therefore a lower "salting-out" effect on hydrophobic molecules. This ensures maximum solubility during elution and improves

recovery." (see page 38, heading "Counter-Ions"). Hence, there was a clear suggestion in the art to use NaCl for IEX, i.e. ion exchange chromatography.

Since the botulinum toxin preparation defined in claim 2 comprising at least Zn, Fe and Mg ion concentrations could not be assigned a technical effect, the difference was simply an arbitrary modification which could not establish an inventive step.

Consequently, the subject matter of claims 1 and 2 lacked an inventive step over document D23 in combination with document D8.

- XI. Appellant requested that the decision under appeal be set aside and the patent be revoked.

- XII. Respondent requested that the appeal be dismissed, or alternatively, that the decision under appeal be set aside and the patent be maintained on the basis of auxiliary requests 2 or 3 filed on 7 January 2019.

Reasons for the Decision

- 1. The respondent made no substantive submissions in appeal proceedings, neither in reply to the statement of grounds of appeal nor to the board's communication. The board had duly taken the appellant's submissions into account and provided its preliminary opinion on the case in such communication. The appellant did not reply in substance to the board's communication. Hence, the board has no reason to change its view expressed in it and can issue the present decision in writing.

Main request (claims 1 to 4) - (Auxiliary request 1 as maintained by the opposition division).

2. The appellant raised objections under Articles 56, 84, 123(3), and 83 EPC. However, in view of the board's conclusion on inventive step of the main request (infra), there is no need to enter into a discussion of the merits of the other objections.

Inventive step (Article 56 EPC)

Closest prior art

3. In opposition proceedings, it was common ground between the parties that document D23 represents the closest prior art with regard to the method of claim 1 and the non-spreading botulinum toxin preparation according to claim 2.

- 3.1 Document D23 relates to the preparation and characterization of homogeneous neurotoxin type A from *Clostridium botulinum*. It discloses the isolation of haemagglutinin-neurotoxin complexes (see Title, abstract point 1). The botulinum toxin is obtained from culture medium by acid precipitation, clarified by centrifugation, homogenized, re-extracted with buffer, pooled and incubated with ribonuclease. The ammonium sulfate sedimented toxin is redissolved in 50-100 ml 0.05 M sodium citrate buffer, pH 5.5, and dialysed against this solution at 4 °C. The brown pigment is removed by adding a half volume of swollen DEAE-Sephadex A-50. The clear solution is then loaded onto a column (90 x 8 cm) of DEAE-Sephacel equilibrated with the latter buffer; The toxin is eluted in the void volume and fractions having a 260/280 nm absorbance ratio of 0.54-0.58 were pooled (see page 494, col.1, "Isolation of Haemagglutinin-Neurotoxin Complexes", Table 1).

- 3.2 Starting from document D23, the opposition division defined the technical problem to be solved as the provision of a method for obtaining botulinum toxin products with an improved therapeutic range.
- 3.3 Appellant contended that the method according to claim 1 differed from the method of document D23 in that it related to a method for purifying a "non-spreading" botulinum toxin and in that the method used a buffer with 0.02-0.2 M of sodium chloride (NaCl). The botulinum toxin preparation defined in claim 2 differed from the one in document D23 in that it comprised Zn, Fe and Mg ions at specific concentrations and in that it was explicitly related to a "non-spreading" preparation.

Since the purified toxin obtained in document D23 was not tested for its "non-spreading" activity, this property could not distinguish the process of claim 1 and the product of claim 2 from the prior art process and product.

Despite the critical importance of the pH and the ionic strength of the buffer for ion exchange chromatography, it was neither clear nor had it been demonstrated that the use of an aqueous solution comprising 0.02-0.2 M of sodium chloride (NaCl) or of a 0.05 M sodium citrate buffer at pH 5.5 - taking into account the dissociation of citrate at pH 5.5 - would lead to any difference in the botulinum toxin preparation obtained after elution from the DEAE-Sephadex column.

- 3.4 Since the ionic composition of Allergan's Botox was not determined, no specific effect could be assigned to the ionic composition, as the "subfraction pII obtained in Example 1" could differ from Allergan's Botox reference

preparation by more than just the Zn, Fe and Mg ion concentrations.

- 3.5 Appellant concluded that since no technical effect was clearly assignable to the differences identified above, the objective technical problem had to be reformulated in less ambitious terms as the provision of an alternative botulinum toxin preparation and the provision of an alternative process for purifying a botulinum toxin.
- 3.6 The board agrees that there is no evidence in the patent application - or anywhere else - to demonstrate that the "non-spreading" effect of the botulinum toxin preparation defined in claim 2 is the direct consequence of the different buffer used in the method of claim 1 or the different ionic composition.
- 3.6.1 In consequence, it is not possible, based on the results disclosed in the patent, to conclude that the technical problem defined by the opposition division was actually solved (see test Examples 2 and 3 and Figs 5 to 8).
- 3.7 Indeed, each of the two freeze-dried products (Allergan's Botox and the pII fraction) were dissolved in 10 ml of distilled water (see patent, test Example 3). Their ion contents were then measured using an inductively coupled plasma mass spectrometer (see Table 7). The content of ions of the pII fraction purified by the method of claim 1 is clearly higher than those present in the commercial product. In mass spectrometry, the ions are usually separated on the basis of their mass-to-charge ratio whereas the detector receives an ion signal that is proportional to the concentration of the tested solution (freeze-dried

in 10 ml). Since the content of ions in the preparation of claim 2 is defined per 100 U/ml, it is unclear whether the reduced spread/*diffusion* of the active fraction pII may be supported by the effect assigned to the content of ions measured at a concentration of 100 U/10 ml (see Table 7). This view has been not contested.

3.8 Hence, the technical problem is indeed formulated as the provision of an alternative botulinum toxin preparation and an alternative method of purifying the same.

3.9 The solution is the method of claim 1 and the non-spreading botulinum toxin preparation of claim 2.

Obviousness

3.10 It remains to be assessed whether the skilled person starting from the method or botulinum toxin preparation of the closest prior art and faced with the technical problem identified above would have arrived at the claimed method or the claimed preparation in an obvious manner.

3.11 Document D8 explicitly mentions that "The counter-ions (salt ions) used in IEX are almost always Na⁺ for cation exchange and Cl⁻ for anion exchange." (see page 38, heading "Counter-Ions"). Hence, there is a clear suggestion to use NaCl for IEX, i.e. ion exchange chromatography.

3.12 Starting from the content of document D23, the skilled person faced with the problem of providing an alternative method of purifying botulinum toxin, without any particular effect, would have obviously

replaced the sodium citrate buffer pH 5.5 by another buffer comprising NaCl, as disclosed in document D8 on page 38.

The method for purifying a botulinum toxin according to claim 1 and the botulinum toxin preparation defined in claim 2 are therefore obvious for a skilled person in the light of the teachings of documents D23 and D8.

Hence, the main request lacks an inventive step.

Auxiliary requests 2 and 3 filed during opposition proceedings on 7 January 2019.

4. Since claim 1 of the main request and auxiliary requests 2 and 3 is identical, the objections under Article 56 EPC set out above for the method according to claim 1 of the main request also apply mutatis mutandis to the method according to claim 1 of auxiliary requests 2 and 3.
5. The board concludes that auxiliary requests 2 and 3 contravene Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



L. Malécot-Grob

B. Stolz

Decision electronically authenticated