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Datasheet for the decision of 18 June 2021

Case Number: T 1483/18 - 3.3.07

Application Number: 05757842.9

Publication Number: 1817051

IPC: A61K38/48, A61K47/30

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITIONS COMPRISING BOTULINUM NEUROTOXIN, A NON IONIC SURFACTANT, SODIUM CHLORIDE AND SUCROSE

Patent Proprietor:
Ipsen Biopharm Limited

Opponents:
Merz Pharma GmbH & Co. KGaA
ALLERGAN, INC.
Daewoong Pharmaceutical Co., Ltd.

Headword:
Botulinum neurotoxin composition / IPSEN

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

Keyword:
Amendments - added subject-matter (no)
Sufficiency of disclosure - (yes)
Novelty - implicit disclosure (no)
Inventive step - (yes)

Decisions cited:
T 1063/07

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Beschwerdekammern

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Case Number: T 1483/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 18 June 2021

Appellant: (Opponent 2)	ALLERGAN, INC. 2525 Dupont Drive Irvine CA 92612 (US)
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Respondent: (Patent Proprietor)	Ipsen Biopharm Limited Ash Road, Wrexham Industrial Estate, Wrexham LL13 9UF (GB)
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Party as of right: (Opponent 1)	Merz Pharma GmbH & Co. KGaA Eckenheimer Landstrasse 100 60318 Frankfurt/Main (DE)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 April 2018 concerning maintenance of the European Patent No. 1817051 in amended form.**

Composition of the Board:

Chairman A. Usuelli
Members: E. Duval
A. Jimenez

Summary of Facts and Submissions

I. European patent 1 817 051 ("the patent") was granted on the basis of 23 claims. Claim 1 of the patent related essentially to a solid or liquid pharmaceutical composition comprising a botulinum neurotoxin complex, a surfactant, sodium chloride, a buffer, and no albumin.

II. Three oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed.

III. The opposition division took the interlocutory decision that, on the basis of the main request filed during the oral proceedings, the patent met the requirements of the EPC.

Claims 1 and 2 of this main request read as follows:

"1. A liquid pharmaceutical composition comprising:
- botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F, or G),
- a non-ionic surfactant as a stabilizing agent,
- sodium chloride, and
- a buffer to maintain pH between 5.5 to 7.5

wherein said liquid pharmaceutical composition does not comprise albumin."

"2. A liquid pharmaceutical composition according to claim 1, wherein said composition consists of:

- botulinum neurotoxin complex (type A, B, C, D, E, F or G) or high purity botulinum neurotoxin (type A, B, C, D, E, F, or G),
- a non-ionic surfactant,
- sodium chloride, and
- a buffer to maintain pH between 5.5 to 7.5,
- water, and

optionally

- a disaccharide."

IV. The decision of the opposition division made reference in particular to the following documents:

D1: WO 2005/007185
D2: WO 01/58472
D4: US2003/0224020
D7: Declaration J. Richard During Prosecution US 11/632,156
D10: US 2003/0118598
D11: Chi et al., *Physical Stability Of Proteins In Aqueous Solution [...],* Pharmaceutical Research, 2003, 20(9), p.1325-1336
D20: US 2003/0138437
D21: US2002/0107199
D22: WO99/037326
D23: US5,981,485
D24: EP1016673
D25: EP0627924
D45: DasGupta B. et al., *Toxicon*, 22(3), p. 415-424, 1984

V. In particular, the opposition division decided that:

(a) The main request did not comprise added subject-matter. The feature of claim 1 regarding the absence of albumin was derivable from the

disclosure, in the application as filed, that albumin is replaced by a surfactant. In claim 2, the word "consisting" derived from the terms "containing" or "comprising" originally used.

(b) The subject-matter of the main request was sufficiently disclosed. In particular, the term "non-ionic surfactant as stabilizing agent" did not lead to an insufficiency of disclosure.

(c) The subject-matter of the main request was novel over D1, because it had not been shown that the botulinum toxin compositions of D1 inevitably comprised NaCl.

(d) Regarding inventive step, D2 could be considered as closest prior art. D2 did not disclose liquid pharmaceutical botulinum neurotoxin formulations comprising a non-ionic surfactant. The objective technical problem was to modify D2 to provide for stable liquid ready-to-use botulinum neurotoxin formulations. The claimed solution was not obvious in light of D11, D10 or D20-D22.

Likewise, the claimed invention was not obvious when starting from D4 as closest prior art, because D4 was not concerned with the stabilization of liquid pharmaceutical compositions but with lyophilization for storage.

VI. Opponent 2 (appellant O2) and opponent 3 (appellant O3) respectively lodged an appeal against the decision of the opposition division.

VII. With its reply to the grounds of appeal, the patent proprietor (respondent) defended its case on basis of

the main request upheld by the opposition division and on the basis of auxiliary requests 1-3 filed with said reply.

VIII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA issued on 2 March 2021. In its preliminary opinion, the Board expressed in particular doubts as to the compliance of claim 9 of the main request with Article 123(2) EPC.

IX. By letter dated 16 June 2021, the respondent submitted an amended main request and an amended auxiliary request 1. The amended main request was identical to the main request upheld by the opposition division (see III. above), apart from the deletion of claim 9.

X. Oral proceedings were held before the Board.

XI. Appellant O2 and appellant O3 both request that the decision under appeal be set aside and that the patent be revoked. They further request that auxiliary requests 1-3 filed by the respondent on 16 June 2021 or with its reply to the grounds of appeal not be admitted into the proceedings.

XII. The respondent requests that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed with the letter of 16 June 2021, or, alternatively, on the basis of auxiliary request 1 filed on 16 June 2021 or of one of auxiliary requests 2-3 filed with its reply to the grounds of appeal.

XIII. The party as of right (opponent 1) did not file any request nor any submission in the appeal proceedings.

XIV. The arguments of appellants O2 and O3 regarding the main request can be summarised as follows:

(a) Added subject-matter

The requirement of claim 1 regarding the absence of albumin did not derive directly and unambiguously from page 1 line 26 to page 2 line 21 of the application as filed. The correct reading of this passage revealed that the application did not seek to replace albumin in general but only specific types of albumin, in particular animal derived albumin. Furthermore, this passage related to the replacement not only of albumin, but also of polysaccharides or trehalose, neither of which were excluded from the compositions of claim 1.

Claim 1 also added matter because it resulted from the combination, in the application as filed, of at least claims 1, 2, 3, 4, page 2, lines 14 and 15, page 5, line 2, page 6 line 4 together with the selection of liquid compositions over the solid compositions.

The feature "non-ionic surfactant as a stabilizing agent" could not be derived from the first paragraph on page 5 together with the second paragraph on page 6, as these passages were not linked. The application as filed did not disclose that a non-ionic surfactant *per se* qualified as stabilising agent.

The word "consisting" in claim 2 was not directly and unambiguously disclosed by the word "comprising" in the application as filed, following the reasoning of T 1063/07. The option of claim 2 lacking the disaccharide, which was present in all examples, was not derivable from the application as filed.

(b) Sufficiency of disclosure

D7 proved that, at concentrations of surfactant lower than the critical micellar concentration (cmc), the botulinum toxin denatured, and thus the compositions were not effective. The surfactant only operated effectively as a stabilising agent when present in concentrations above the cmc. As a result, the claims, which were not limited to a concentration of surfactant above the cmc, could not be worked across their scope. Furthermore, the wording "non-ionic surfactant as stabilizing agent" stated in essence that each and every non-ionic surfactant could be used as a stabilizing agent. Considering the reduced support provided by the examples, which were purely prophetic ones, finding a suitable non-ionic surfactant which provided a stabilizing effect amounted to a research program.

(c) Novelty

The subject-matter of claim 1 lacked novelty over the 2nd entry in Table 1 on page 11 of D1. This example comprised in particular a liquid composition containing botulinum toxin type A. D1 disclosed on page 10, third paragraph, that the neurotoxin type A could either be obtained from List Biological Laboratories Inc., Campbell, California, USA or be produced according to D45. In D45, the final stage of the neurotoxin preparation involved an elution with an equilibrating buffer containing NaCl. Accordingly, the presence of NaCl was implicitly disclosed in D1.

(d) Inventive step

D2 could be selected as a closest prior art document.

Example 5 of D2 disclosed a composition undergoing a lyophilisation, and therefore disclosed a liquid pharmaceutical composition. The composition of example 5 comprised botulinum toxin type A, sodium chloride (due to the reference to example 1, which included saline), histidine, and no albumin. D2 (see page 34) also disclosed ready to use liquid pharmaceutical compositions, and made clear that the stabilising excipients used in the lyophilised compositions could be used in these liquid formulations.

The distinguishing feature of the invention was merely the non-ionic surfactant. There was no evidence to demonstrate that this distinguishing feature led to an improved technical effect over the subject matter of D2.

The objective technical problem was the provision of an alternative composition comprising botulinum toxin.

The claimed solution was obvious in light of D2 alone, which taught that surfactants could be used to reduce adsorption in liquid compositions (see page 34, lines 19-20), hence stabilising botulinum toxin (see page 25, lines 10-20; page 2, lines 17-25). D10 (see example 8 and paragraph [0202]) and D20 contained a teaching similar to that of D2, and, in addition, specifically referred to the non-ionic surfactant polysorbate P80 as a secondary stabilizer to be used alone or in combination with primary stabilizers (see paragraph [0114] of D10). D10 would therefore have taught the person skilled in the art that a non-ionic surfactant could be incorporated into the botulinum-containing composition of Example 5 of D2. D11 (see page 1328) and D21 (see paragraph 122), as well as D4, also provided

an incentive to add a non-ionic surfactant as stabilisers.

Alternatively, D4 could be used as closest prior art. D4 dealt with the stabilization of botulinum neurotoxin and stated that it would be advantageous to replace albumin as stabilizing excipient from the compositions. D4 disclosed the surfactant non-ionic phosphatidyl choline as stabilizing agent. Furthermore, the composition of example 1 of D4 contained NaCl, a phosphate buffer to maintain the pH between 7.0 and 7.4, and did not comprise albumin.

The difference between D4 and the claimed invention was that liquid pharmaceutical compositions were to be stabilized in contrast to lyophilized forms. There was no apparent effect associated with this difference.

The objective technical problem was the provision of an alternative status form (liquid) of a pharmaceutical composition described in the prior art. The claimed solution did not involve an inventive step because D4 indicated that the lyophilized compositions could be reconstituted and thus be provided in a liquid form.

Thus the main request did not meet the requirements of inventive step.

XV. The respondent's arguments regarding the main request can be summarised as follows:

(a) Added subject-matter

Claim 1 found basis on page 7, lines 25-33 of the application as filed (see also claim 1, 3 and 4). The feature of claim 1 regarding the presence of a

surfactant as a stabilizing agent and the absence of albumin was directly and unambiguously derivable from page 1, lines 29-31 and page 2, lines 13-14. The non-ionic surfactant was disclosed as a preferred embodiment on page 6, line 4. Therefore, there was no undisclosed combination of features in claim 1 of the main request.

In claim 2 of the main request, the replacement of the term "comprising" with "consisting" was supported in the application as filed, since no further ingredients were listed in the application as filed as essential components, in contrast to the situation in T 1063/07. Due to the optional presence of a disaccharide, claim 2 covered two embodiments: one in which the liquid pharmaceutical composition consisted in (a) the botulinum neurotoxin, (b) a surfactant, (c) sodium chloride, (d) the buffer and water, supported by page 8, lines 5-11 of the application as filed, and a second embodiment in which the liquid pharmaceutical composition consists in the same components plus a disaccharide, supported by the passage on page 9, line 13-15 of the application as filed. The main request therefore met the requirements of Article 123(2) EPC.

(b) Sufficiency of disclosure

The burden of proof rested on the respondents to demonstrate that there were serious doubts, substantiated by verifiable facts, that the invention was insufficiently disclosed. D7, on which the respondents relied, did not provide any proof that the person skilled in the art would be unable to prepare compositions falling within the claims. D7 only demonstrated that above the cmc, the surfactants worked differently than a polysaccharide. The description and

the examples of the patent provided sufficient teaching for the person skilled in the art in this regard.

(c) Novelty

D1 did not described that the composition of entry 2 in Table 1 of Example 1 contained NaCl. There was no direct and unambiguous disclosure in D1 that the botulinum neurotoxin type A used in Entry 2 in Table 1 would be produced according to D45. In addition, D45 related to the purification of botulinum neurotoxin type A involving several stages, including an elution using an NaCl buffer. Further steps were missing in order to provide the neurotoxin in the appropriate dilution specified in D1. Hence NaCl was not inevitably present. Hence the claimed subject-matter was novel.

(d) Inventive step

Regarding inventive step starting from D2, example 5 of D2 described a lyophilized or vacuum-dried pharmaceutical composition comprising botulinum neurotoxin and sodium chloride, histidine and hetastarch as stabilizing agent, in the absence of blood-derived albumin. The subject-matter of claim 1 differed at least in that:
- it comprised a non-ionic surfactant as a stabilizing agent,
- it comprised a buffer to maintain pH between 5.5 and 7.5, and
- it was in liquid form.

The objective technical problem was the provision of stable, liquid pharmaceutical compositions comprising botulinum neurotoxin, in the absence of albumin.

Considering the statement in D2 (see page 15, lines 14-18), the skilled person would have been very reluctant to modify the lyophilized pharmaceutical compositions of D2. In addition, D2 (page 34, line 9) did not suggest the use of non-ionic surfactants. The same conclusions applied for D10 and D20-D22, none of which was concerned with the stabilization of liquid pharmaceutical compositions

As to D4, it described albumin-free lyophilized botulinum neurotoxin compositions. The subject-matter of claim 1 differed at least in that it comprised a non-ionic surfactant as a stabilizing agent, and it was in liquid form.

The objective technical problem is the provision of stable, liquid pharmaceutical compositions comprising botulinum neurotoxin, in the absence of albumin.

Starting from D4, the skilled person would have found no incentive to use a non-ionic surfactant in order to stabilize a liquid composition comprising botulinum neurotoxin.

Thus, the subject-matter of the main request met the requirements of inventive step.

Reasons for the Decision

Main request

1. Article 123(2) EPC

1.1 Claim 1

1.1.1 Claim 1 requires that the liquid composition comprises a surfactant and does not comprise albumin. The Board agrees with the opposition division that the absence of albumin can be derived from page 1, line 26, to page 2, line 17 of the application as filed, and in particular from the mention of known concerns about albumin and from the following statements:

"Currently, the marketed botulinum neurotoxin compositions contain human serum albumin. However, some concerns have been expressed about albumin (see e.g. in PCT application WO 01/58472). [...]
The Applicant has unexpectedly discovered that a surfactant possesses sufficient stabilising effects to replace albumin, the polysaccharide of PCT patent application WO 01/58472 or the trehalose of PCT patent application WO 97/35604 in botulinum neurotoxin compositions."

According to the appellants, this statement regarding the replacement of albumin does not unambiguously refer to albumin in general, but is rather to be interpreted as referring only to the specific albumin mentioned in WO 01/58472 (i.e. D2), or to the human serum albumin contained in the marketed botulinum neurotoxin compositions.

The Board does not share the view of the appellants. Firstly, the above passage mentions that a surfactant may replace a specific polysaccharide (of WO 01/58472) or a specific trehalose (as in WO 97/35604), but remains general as regards albumin, i.e. it discloses the ability of surfactants to replace albumin without limiting this albumin to that of D2 or in the marketed compositions. Secondly, the concerns mentioned earlier in the same passage concern albumin in general, and the reference to D2 is only made by way of example (using the abbreviation "e.g."). There is thus no reason to read the above statement in the application as filed otherwise than literally, i.e. the application as filed discloses that the surfactant may replace albumin in general.

The fact that claim 1 of the main request excludes the presence of albumin but not the presence of a polysaccharide or of trehalose does not introduce added subject-matter either, since the absence of these respective stabilisers and their replacement with the surfactant are presented as alternatives in the above passage.

1.1.2 The Board also shares the opinion of the opposition division that the feature "a non-ionic surfactant as a stabilizing agent" finds basis on page 5, lines 1-2 ("the surfactant will be such that it stabilises the botulinum toxin") and page 6, line 4 ("Preferably, the surfactant will be a non-ionic surfactant"). These two statements unambiguously refer to "the surfactant" which is present in the compositions according to the invention, i.e. they refer to the same surfactant being non-ionic and acting as a stabilizing agent.

The combination of features in claim 1 is not seen as introducing added subject-matter, considering the preference expressed in the application as filed for NaCl as crystalline agent, the pH range (see claims 1, 3 and 4) and non-ionic surfactants (page 6, line 4).

1.2 Claim 2

1.2.1 Dependent claim 2 relates to a liquid pharmaceutical composition consisting of (a) the botulinum neurotoxin complex, (b) a non-ionic surfactant, (c) sodium chloride, (d) the buffer, water, and optionally a disaccharide. Thus claim 2 defines two alternative subject-matters, namely compositions with or without disaccharide. The first alternative derives from the passages on page 8, lines 5-11, disclosing compositions containing components (a)-(d) and water. The second alternative finds support on page 9, lines 13-15, according to which the "formulation according to the invention may contain a disaccharide".

1.2.2 In both passages on pages 8 and 9 of the application as filed, the expression "containing" is used, which allows for the presence of any further component. In contrast, in both alternatives of claim 2 of the main request, the expression has been amended into "consisting of", thus excluding the presence of further components in the composition.

This amendment does not introduce added subject-matter for the following reasons. Regarding the above second alternative of present claim 2, the application as filed teaches on page 8 that the composition may be obtained by mixing components (a)-(d) and water, and the (optional) presence of a disaccharide is mentioned on page 9. The application as filed does not disclose

any further essential components which must be included, and the possibility for the composition to consist only of components (a)-(d), water and the disaccharide is confirmed by the examples (see pages 23-24 of the application as filed). As to the first alternative, disaccharides are not mentioned among the components recited on page 8, and the fact that the presence of the disaccharide is optional is unambiguously derivable from page 9 (in particular the wording "may contain a disaccharide"). Accordingly, both alternatives of claim 2 are directly and unambiguously derivable from the application as filed.

The appellants expressed the view that the approach set out in T 1063/07 should be followed in the present case. In T 1063/07, the competent Board found that the replacement of "comprising" by "consisting of" contravened Article 123(2) EPC because there was no clear and unambiguous disclosure in the application as originally filed of a catalyst composition consisting of a metal complex and an activating cocatalyst. It could not be derived from the application as filed that no other component, in particular no diluent, should be present.

However, under Article 123(2) EPC, the question whether an amendment, be it a change of "comprising" or "containing" into "consisting of" or otherwise, remains within the limits of what a skilled person would derive directly and unambiguously from the application as filed can only be answered by reference to the application in question, i.e. on the merits of the specific case. Here, the Board considers that the situation differs from that of T 1063/07. In particular, the absence of disaccharide from the liquid composition is considered in the application as filed,

for the reasons given above. The Board concludes that the amendment does not introduce added subject-matter.

1.3 Accordingly, the criteria of Article 123(2) EPC are met.

2. Sufficiency of disclosure

Claim 1 specifies that the composition comprises a non-ionic surfactant as a stabilising agent. The question is whether the patent enables the skilled person to prepare compositions in which the surfactant exhibits this stabilising property.

The patent describes in the examples some ways to carry out the invention, namely examples 2 and 3 comprising polysorbate 80 as non-ionic surfactant. Despite the absence of the known stabilisers albumin or the polysaccharide hetastarch, these exemplified liquid compositions are shown to be stable (see paragraphs [0043] and [0045], "it is stable for at least six months at 23 to 27°C and at least twelve months at 2-8°C"; see additionally paragraphs [0030] and [0048] for the assessment of stability). The respondents asserted that these examples are merely prophetic. The Board does not agree and sees no reason to consider the stability levels reported in the patent as being unreliable. It is furthermore well established that an objection of lack of sufficiency of disclosure presupposes that there are serious doubts, substantiated by verifiable facts. Here, the appellants did not explain further why the results given in the patent for a composition comprising polysorbate 80 could not be reproduced with other non-ionic surfactants. Nor did the appellants show that the

stability of the exemplified compositions was due to their sucrose component rather than to the surfactant.

The appellants see in declaration D7 (see paragraph 10) a demonstration that surfactants at concentrations below the cmc do not have stabilising properties. Consequently, many compositions covered by claim 1, which is not limited by the concentration of the surfactant, would be incapable of stabilizing the botulinum toxin. The Board is not convinced. The purpose of the declaration D7 was to explain why it was not obvious to replace the albumin or polysacchaiides present in prior art botulinum formulations by a non-ionic surfactant as stabilizing agent. At paragraph 10 of D7, a mechanistic explanation is given for the stabilising effect of these surfactants at concentrations above the cmc, namely the full saturation of the liquid-solid and liquid-gas interfaces. This saturation avoids any interaction of the botulinum toxin with these interfaces that would result in a modification of its three dimensional active conformation. There is however no evidence or statement in D7 to the effect that, at concentrations below the cmc, non-ionic surfactants are devoid of any stabilising properties.

Accordingly, the main request meets the requirements of sufficiency of disclosure.

3. Novelty

3.1 D1 discloses (see example 1, page 10 and 2nd entry in table 1 on page 11) a liquid composition containing botulinium toxin type A, polysorbate 20 and sodium phosphate. The presence of NaCl in the composition,

required by present claim 1, is not explicitly disclosed in D1.

In D1 (see page 10), the toxin is either obtained from "List Biological Laboratories, Inc. Campell, California, USA" or produced according to D45. The appellants argue that, in the final stage 7 of the preparation method of D45, the toxin is eluted with an NaCl buffer. Consequently the presence of NaCl in the toxin would be implicit. There is however no evidence of the presence of NaCl in the other alternative of D1, i.e. in the toxin obtained from List Biological Laboratories.

3.2 According to established case law, an alleged disclosure can only be considered "implicit" if it is immediately apparent to the skilled person that nothing other than the alleged implicit feature forms part of the subject-matter disclosed (see the Case Law of the Boards of Appeal, 9th edition 2019, I.C.4.3). Implicit disclosure means disclosure which any person skilled in the art would objectively consider as necessarily implied in the explicit content.

3.3 Here, contrary to the appellants' view, the relevant question is not whether the use of botulinum neurotoxin obtained according to D45 is part of the disclosure of D1, but whether, following D1, the neurotoxin used in the particular entry 2 of table 1 of example 1 was necessarily obtained using the particular procedure of D45, as opposed to being obtained from List Biological Laboratories. Since D1 does not contain any information to that effect, novelty over D1 must be acknowledged for this reason already.

3.4 In addition, the composition of example 1 of D1 is prepared starting from a solution of Clostridium botulinum Neurotoxin Typ A having a concentration of 168 µg/ml (see D1, page 10). However, even if it were assumed that the neurotoxin of entry 2 in example 1 of D1 was produced as in D45, there is no indication that the method of D45 would lead to this particular concentration. As noted by the opposition division, D1 does not disclose how the stage 7 eluate of D45 is handled to provide the solution comprising the neurotoxin at 168 µg/ml. Thus, one or more undisclosed further step(s) would be necessary in order to reproduce D1. It does not inevitably follow from D1 that, despite these undisclosed further steps, NaCl is present in the neurotoxin used in entry 2 of table 1.

3.5 Accordingly, the subject-matter of claim 1 of auxiliary request 2 is novel.

4. Inventive step

4.1 Starting from D2, D10 or D20

4.1.1 All parties agree that D2 represents a suitable starting point for the assessment of inventive step. The disclosures of D10 and D20 are similar to D2.

D2 is concerned with botulinum toxin pharmaceutical compositions free of blood derived albumin (see abstract). D2 generally envisages both solid and liquid formulations, for instance as single-step presentations, e.g. pre-filled syringes (see page 34 lines 9 - page 35 line 27).

D2 discloses (see example 5, referring to example 1) an albumin-free pharmaceutical composition comprising

botulinum neurotoxin, sodium chloride (from the saline used prior to lyophilisation in example 1), histidine and hetastarch (as stabiliser). Although example 5 assesses the stability of the formulation in lyophilised state only, the Board agrees with the appellants that it also implicitly, but necessarily, discloses the composition in liquid form, i.e. before lyophilisation or after reconstitution for administration.

The same teaching is provided in D10 (see paragraphs [0202]-[0203] and examples 8 and 1) and in D20 (see paragraphs [0156]-[0157] and examples 8 and 1).

4.1.2 The claimed subject-matter differs at least by the presence of a non-ionic surfactant as a stabilising agent.

The appellants contest that this difference leads to any technical effect. The Board agrees that no improvement has been shown to result from the presence of the non-ionic surfactant in comparison with the composition of D2. Nonetheless, the stabilising effect of the non-ionic surfactant is a feature of claim 1. The achievement of this effect is corroborated by examples 2 and 3 of the patent (see 2. above). Thus, for the purposes of inventive step, the Board accepts that the claimed subject-matter is characterised by a stabilising effect of the non-ionic surfactant, even if it is not to an improved level.

4.1.3 Accordingly, as submitted by the respondent, the objective technical problem is the provision of stable, liquid pharmaceutical compositions comprising botulinum neurotoxin, in the absence of albumin. For the reasons

given above (see 2.), the Board accepts that this problem has been solved.

4.1.4 For the following reasons, the skilled person starting from example 5 of D2 would not have expected the claimed liquid albumin-free composition to solve this problem.

Example 5 of D2 pertains in the first place to a solid, lyophilised albumin-free botulinum toxin composition. A liquid composition is disclosed in example 5, but only as intermediate in the preparation of the final lyophilised composition. The data regarding stability of the composition in example 5 are given only for the solid composition. Furthermore, D2 does not credibly show that stability results obtained in the solid form could be extrapolated to liquid compositions. On the contrary, D2 points out not only the particular difficulty of stabilising botulinum toxin (see page 15, lines 14-18) but also the particular sensitivity of liquid formulations (see page 34, lines 14-18). Furthermore, D2 does not generally show or state that stabilizing excipients used in freeze-dried formulations would be also effective in liquid formulation, but only that they "might be adapted" for such a use (see D2, page 34, lines 19-24). Thus, contrary to the appellants, the Board does not see in example 5 of D2 a disclosure of stable liquid botulinum toxin compositions comprising substitutes for albumin.

The appellants expressed the view that surfactants were known to reduce absorption and therefore avoid botulinum toxin denaturation and loss (see D2, page 34, lines 19-20 in combination with page 25, lines 10-20). However, while the skilled person might expect this mechanism to contribute to stabilisation of the toxin,

a sufficient stabilisation in the context of a liquid botulinum toxin lacking any albumin could not be anticipated. Likewise, D10 (see paragraph [0114]) and D20 (paragraph [0098]) indicate that additional stabilizers such as the non-ionic surfactant polysorbate (i.e. P80) may be used alone or in combination with primary stabilizers, such as proteins and polysaccharides. D10 and D20 do not however teach that this non-ionic surfactant would stabilise the toxin in a liquid albumin-free formulation. Neither is this effect taught by D11 (see page 1328), D21 (see paragraph [0122]), D22 (see page 22, lines 16-17), D23 (see the abstract), D24 (see the abstract), D25 (see paragraph [0001]) or D4 (see 4.2 below).

4.2 Starting from D4

D4 discusses that botulinum neurotoxins are very susceptible to denaturation by several mechanisms, and that all of the lyophilized preparations contain human albumin as a stabilizing excipient. It further states that it would be advantageous to replace albumin as stabilizing excipient from the compositions (see paragraph [0019]). Thus D4 considers the issue of stability only in the context of solid formulations. The Board agrees with the opposition division that D4 does not address the problem of providing stable liquid botulinium toxin formulations.

The objection of the appellants starting from D4 is based on example 1, which discloses the preparation of a lyophilised albumin-free botulinum toxin formulation comprising phosphatidyl choline as stabilizing agent. Even if D4 discloses liquid formulations resulting from the reconstitution of this lyophilised composition (see paragraph [0048]), the stability of these liquid

formulation is not addressed in D4. Accordingly, D4 does not disclose either any stable liquid botulinum toxin compositions comprising substitutes for albumin. To the extent that the skilled person would consider D4 as a starting point when seeking stable liquid albumin-free botulinum toxin formulation, the claimed solution would not be obvious for the same reasons as given above (see 4.1).

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 on the basis of the claims of the main request filed with letter of 16 June 2021 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated