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Datasheet for the decision of 21 October 2021

Case Number: T 0406/17 - 3.3.07

Application Number: 05765454.3

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Language of the proceedings: EN

Title of invention:
THERAPEUTIC COMPOSITION WHIT A BOTULINUM NEUROTOXIN

Patent Proprietor:
Merz Pharma GmbH & Co. KGaA

Opponent:
ALLERGAN, INC.

Headword:
Composition with a botulinum neurotoxin / MERZ PHARMA

Relevant legal provisions:
RPBA 2020 Art. 11, 25(1), 12(2)
EPC Art. 100(c), 123(2), 111(1)

Keyword:
Amendments - extension beyond the content of the application as filed (no)
Remittal - special reasons for remittal

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D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 October 2021

Appellant: (Patent Proprietor)	Merz Pharma GmbH & Co. KGaA Eckenheimer Landstrasse 100 60318 Frankfurt (DE)
Representative:	Ricker, Mathias Wallinger Ricker Schlotter Tostmann Patent- und Rechtsanwälte Partnerschaft mbB Zweibrückenstrasse 5-7 80331 München (DE)
Respondent: (Opponent)	ALLERGAN, INC. 2525 Dupont Drive Irvine CA 92612 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 2 December 2016 revoking European patent No. 1786459 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	F. Bostedt

Summary of Facts and Submissions

I. European patent 1 786 459 (hereinafter "the patent") was granted on the basis of 8 claims. The independent claims 1 and 5 of the patent as granted read as follows:

"1. A pharmaceutical composition consisting of at least one botulinum neurotoxin selected from *Clostridium botulinum* of types A, B, C1, D, E, F and G, wherein said at least one neurotoxin is free of hemagglutinins and non-toxic non-hemagglutinating proteins, a non-proteinaceous stabilizing agent consisting of polyvinylpyrrolidone, which retains the biological activity of the botulinum neurotoxin in an aqueous solution, a polyalcohol cryoprotectant and optionally a pH buffer, wherein said composition is free from albumin and gelatin and is lyophilized, vacuum dried, reconstituted or in solution."

"5. A method for stabilizing a pharmaceutical composition comprising at least one botulinum neurotoxin selected from *Clostridium botulinum* of types A, B, C1, D, E, F and G, wherein said at least one neurotoxin is free of hemagglutinins and non-toxic non-hemagglutinating proteins, consisting of intermixing said at least one neurotoxin with a non-proteinaceous stabilizing agent consisting of polyvinylpyrrolidone, a polyalcohol cryoprotectant and optionally a pH buffer in an aqueous solution in an amount effective to retain the biological activity of the neurotoxin in the aqueous solution, wherein the resulting composition is free of serum albumin and gelatin."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, the invention was not sufficiently disclosed and its subject-matter extended beyond the content of the application as originally filed.

III. The opposition division decided to revoke the patent. This decision was based on the patent as granted as a main request and on auxiliary requests I-VI, wherein auxiliary request I, V and VI were filed on 19 July 2016 and auxiliary requests II-IV were filed during first instance's oral proceedings on 20 September 2016.

The opposition division decided *inter alia* that the subject-matter of the granted claims was not directly and unambiguously derivable from the original application. In particular the replacement of "comprising" with "consisting of" would limit the claims to botulinum neurotoxin compositions free of sodium chloride and such compositions were not originally disclosed in the patent application. The subject-matter of granted claims 1 and 5 did thus not comply with the requirements of Article 123(2) EPC.

IV. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division.

V. With its statement setting out the grounds of appeal the appellant defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1-5 filed therewith.

VI. Oral proceedings were held before the Board on 21 October 2021.

VII. The appellant requested that the decision under appeal be set aside and the patent be maintained as granted (main request) or that the patent be maintained on the basis of one of the auxiliary requests 1-5 filed with the statement setting out the grounds of appeal on 12 April 2017.

VIII. The respondent requested that the appeal be dismissed, *i.e.* that the patent be revoked. The respondent further requested that the case be remitted to the department of first instance, should the Board consider that any of the requests fulfilled the requirements of Article 123 EPC. The respondent also requested that auxiliary requests 4-5 not be admitted into the appeal proceedings.

IX. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

The amendments performed in independent granted claims 1 and 5 were based on the original application. In particular the replacement of "comprising" with "consisting in" would not result in subject-matter extending beyond the original disclosure, as a composition containing the claimed components and excluding any further component was derivable from the original application as whole. Hence, the subject-matter of granted claims 1 and 5 did not extend beyond the content of the application as originally filed.

X. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

The subject-matter of granted claims 1 and 5 extended beyond the content of the application as originally filed, for the following reasons:

(a) The wording used to define the neurotoxin in the amended independent claims led to a broader definition than originally disclosed, since complexed neurotoxins together with one uncomplexed neurotoxin were henceforth encompassed.

(b) The various amendments regarding the components of the claimed compositions were not originally disclosed in combination and constituted an unallowable generalisation of the specific examples.

(c) The examples, in particular examples 8A and 8B, as well as paragraph [0077] of the original application disclosed compositions containing further components in addition to the presently claimed ones. Consequently, the original application did not provide support for compositions consisting exclusively of the components listed in the granted independent claims. Hence, the amendment of "comprising" to "consisting in" resulted in subject-matter extending beyond the content of the original application.

Reasons for the Decision

Main request (patent as granted)

1. Amendments

1.1 Granted claim 1 is based on original claim 1 wherein:

(a) the definition of the neurotoxins was amended by:
- replacing "a mixture of two or more" by "at least one" as well as

- replacing "wherein the neurotoxin or mixture of neurotoxins if free of" by "wherein said at least one neurotoxin is free of",

(b) the definition of several components was amended or added (modified definition of the complexing proteins, specific stabilizing agent, presence of a polyalcohol cryoprotectant, optional presence of a pH buffer, absence of gelatin and albumin) and specific physical forms were specified, and

(c) the term "comprising" was replaced by "consisting in".

1.2 During the first instance proceedings the discussion focused mainly on the disclosure of examples 8A and 8B as basis for amended claim 1 in the original application. However, for the purpose of assessing allowability of amendments, the entire content of the original application is to be taken into account.

1.3 Amendment (a)

1.3.1 The original application (claim 1) refers to "A pharmaceutical composition comprising a botulinum neurotoxin [...] or a mixture of two or more botulinum toxins, wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins [...]" (emphasis added). Both parties agreed that, according to this wording, all the botulinum neurotoxins (independently of their number) as previously defined and contained in the composition must be free of complexing proteins. The Board sees no reason to deviate from this interpretation.

1.3.2 Granted claim 1 was reworded as follows: "A pharmaceutical composition consisting of at least one botulinum neurotoxin [...], wherein **said** at least one neurotoxin is free of [...]" (emphasis added).

1.3.3 The respondent argued that granted claim 1 merely required that at least one neurotoxin had to be free of the listed proteins. This meant that in the case of a preparation containing more than one neurotoxin, one had to be free of complexing proteins but the others might be in complexed form. This embodiment extended beyond the content of the original application.

1.3.4 The Board shares the opinion of the opposition division that the expression "said at least one" in granted claim 1, when further defining the neurotoxin as being free of the listed complexing proteins, is decisive. The term "said" provides a direct and unambiguous reference to the "at least one neurotoxin" previously defined. The Board considers that due to this reference, the limitation to neurotoxin being free of complexing proteins applies to the previously defined neurotoxin(s) in general *i.e.* as a group of components independently of their amount. It follows from this interpretation that granted claim 1 also provides that all the botulinum neurotoxins (independently of their number), as previously defined and contained in the preparation, must be free of complexing proteins. Accordingly, this rewording does not lead to any extension of the subject-matter of granted claim 1 beyond the originally claimed one.

1.4 Amendment (b)

1.4.1 The original description, in a part entitled "summary", defines generally the claimed composition and lists a

number of preferred embodiments thereof. Each of these embodiments relate to different individual features of the composition. All the components which have been introduced in or excluded from granted claim 1 compared to original claim 1 are individually disclosed in the "summary" part:
- limitation of the stabilizing agent to polyvinylpyrrolidone (PVP), see paragraph [0020],
- presence of a polyalcohol cryoprotectant, see paragraph [0024],
- optional presence of a pH buffer, see paragraph [0021],
- absence of albumin and gelatin, see paragraph [0038].

1.4.2 The Board considers that the skilled person would directly and unambiguously understand from the structure and content of the description that these embodiments, in so far as they relate to individual features of the composition, may be combined. This is confirmed by the mention of such combinations in a further, more detailed part of the application under the heading "Description" (see, for example, paragraphs [0077] or [0079]) as well as in the examples 8A and 8B.

In this context, the respondent argued that these individual features were so interrelated that only the very specific combinations thereof as disclosed in the examples (*i.e.* specific polyalcohol, presence of a specific pH buffer, amounts of components, presence of water as solvent, ...) were originally contemplated. The Board cannot share this view. The mere fact that these individual features may serve the same purpose, namely stabilising the botulinum neurotoxin, cannot justify such an approach. For the skilled person it is clear that the main purpose of the original application resides in the replacement of the commonly used

mammalian-derived proteinaceous stabilizers gelatin and albumin by non-proteinaceous stabilizers (see in particular last sentence of paragraph [0003] or paragraph [0074]). The skilled person would immediately recognise that further components, such as cryoprotectants and pH buffers in general, may merely additionally contribute to said stability (see for example paragraphs [0075] or [0077]).

1.4.3 Moreover, the replacement of the original functional definition of the complexing proteins ("complexing proteins which naturally form complexes with botulinum neurotoxins") by a more structural definition ("hemagglutinins and non-toxic non-hemagglutinating proteins") is based on the definition of the constituents of botulinum toxin complexes provided in paragraph [0004]. Contrary to the respondent's opinion, this replacement, even when considered in combination with the other amendments, does not introduce new subject-matter as it does not derive from a generalisation of the examples (limited to a specific neurotoxin) but from said general definition.

1.4.4 The last features introduced in claim 1 of the main request define the physical form in which the composition might be formulated, namely "wherein said composition [...] is lyophilized, vacuum dried, reconstituted or in solution". These features are disclosed in original paragraph [0065]. This paragraph is located within the part of the original application entitled "Definitions" and relates to the "pharmaceutical composition" in general. The type of formulation chosen for the pharmaceutical composition is not disclosed in the original application as being related to the components of said composition. The Board considers therefore that said features apply to

each and every composition disclosed in the application. Their introduction in the claims, even in combination with the other modifications, is thus not considered to result in subject-matter being claimed which goes beyond the application as filed.

Regarding this amendment, the respondent contended during the oral proceedings that paragraph [0065] did not refer specifically to compositions of the invention but rather generally defined a pharmaceutical composition. Furthermore, the respondent stated that formulating the composition in the form of a solution was inconsistent with the addition of a cryoprotectant in the composition, as a cryoprotectant would only be useful for lyophilisation *i.e.* as a component of a lyophilised composition. These arguments are however not convincing. The definition provided in paragraph [0065] concerns a term used in the patent, in particular in the claims thereof, so that it cannot be concluded that it does not pertain to the claimed pharmaceutical compositions. In addition, as stated by the respondent itself, a cryoprotectant may be useful when lyophilising a solution. Hence, the Board cannot recognise any inconsistency in the fact of claiming a solution containing a cryoprotectant. The claims, which are directed to a product *per se*, do indeed not limit any further use of the product, such as a subsequent lyophilisation of the claimed solution.

1.4.5 It follows that the present combination of modifications is considered to be directly and unambiguously derivable from the original description based on the above cited passages.

1.5 Amendment (c)

1.5.1 The issue to be considered is whether a pharmaceutical composition consisting of the claimed combination of components, free of albumin and gelatin and in one of the claimed physical form was originally disclosed. In other words, the issue is whether a pharmaceutical composition containing the claimed components, excluding any other component and formulated in one of the claimed forms is directly and unambiguously derivable from the original application.

1.5.2 It is undisputed that the original application does not provide any explicit literal basis for a pharmaceutical composition consisting of the claimed components, *i.e.* excluding any other components. However, apart from the botulinum neurotoxin, a non-proteinaceous stabilizer, a cryoprotectant and an optional pH buffer, the general part of the original description does not mention any further essential components which would have to be included in the pharmaceutical composition. Thus, the skilled person would derive from the general disclosure of the original application that the composition may consist of the specific substances mentioned in claim 1.

In this context, the argument of the respondent made during the oral proceedings regarding the subject-matter of paragraph [0077] is not pertinent. This paragraph relates to "hyaluronic acid or PVP or polyethyleneglycol or mixtures thereof" as non-proteinaceous stabilising agent. According to the respondent, this paragraph, when relating to mixtures of agents, discloses compositions containing a further component in addition to the presently claimed ones. The Board does not share this interpretation. The

mentioned passage clearly and unambiguously defines several alternatives for the type of non-proteinaceous stabilising agent, namely (i) hyaluronic acid alone, (ii) PVP alone, (iii) polyethyleneglycol alone and (iv) mixtures of these agents. Granted claim 1 has been limited to the alternative of PVP alone. In that case ,the embodiment relating to mixtures is *de facto* excluded and irrelevant, so that the argument of the respondent is not convincing.

1.5.3 Furthermore, and contrary to the opinion of the respondent, the Board is not convinced that the examples 8A and 8B provide a different teaching. The Board considers that the skilled person cannot directly and unambiguously derive from said examples that sodium chloride is an essential component of the compositions of the invention, for the following reasons:

(a) Examples 8A and 8B state that "the purified neurotoxin of example 1" was used as starting material and no other component than the presently claimed ones is mentioned as a component of the final compositions. The skilled person reading examples 8A and 8B would thus not understand that any further essential components must be present in the final compositions.

(b) As explained by the respondent, and the Board agrees that, it can be derived from example 1 that sodium chloride might be present in the purified neurotoxin preparation due to the purification method thereof which uses a sodium chloride gradient as elution solvent. It follows that the final solutions of examples 8A and 8B implicitly contain sodium chloride. The Board considers however that this implicit disclosure does not

amount to the disclosure of sodium chloride as a necessary and an essential feature of the presently claimed compositions. The respondent insisted on the fact that all the examples of the original application contained sodium chloride, thus confirming its essential nature. The Board however notes that the situation in the other examples of final compositions (the subject-matters of which do not fall under the granted claims) is the same as in examples 8A and 8B, *i.e.* there is an implicit presence of sodium chloride due to the use of the neurotoxin of example 1 as starting material. The respondent further argued that sodium chloride would not be a minor component of the final preparation of example 1, because of the high concentration used (300mM) and the fact that sodium chloride would have an influence on stability. This argument is however not convincing because the value of 300mM corresponds to the maximum concentration of the gradient used (see paragraph [0092]: "In this case, the bound toxin is eluted from the column using a NaCl gradient (0-300mM)"). This does not necessarily mean that it is the concentration at which the neurotoxin was eluted nor that it is the concentration of sodium chloride in the final preparation at the end of the purification. The final amount of NaCl in the starting neurotoxin used in the examples is not known and the original application does not explicitly teach the use of NaCl at all, let alone for stabilisation purposes.

1.5.4 Accordingly, the Board concludes that, in the present case, the replacement of "comprising" by "consisting of" does not result in the definition of subject-matter

extending beyond the original disclosure taken as a whole.

1.5.5 For the sake of completeness, the Boards notes that, the final compositions of examples 8A and 8B implicitly containing sodium chloride may still be considered to fall under the scope of granted claim 1. The pharmaceutical composition claimed in granted claim 1 is not merely defined by its components. It is additionally defined by its physical form. The components constituting the composition according to granted claim 1 do not contain any solvent system. For the claimed composition to be "in solution", the addition of a solvent system / solution is necessary. It follows that a solution according to granted claim 1 contains the pharmaceutical composition *per se* (which is defined by a closed-ended list of components) and an unspecified solvent system. As aqueous sodium chloride is a common solution for the administration of pharmaceutical compositions in medical applications, it may be considered that formulations containing the components defined in granted claim 1 as well as water and sodium chloride fall under the scope of granted claim 1.

The respondent argued that this interpretation of granted claim 1 would be inconsistent with the use of the wording "consisting of". In its view, merely solvents and not solutes could be added to the claimed composition to formulate it as a solution. The Board does not share this view. The term "consisting" refers to the actual components of the composition *per se*, not to the final solutions. Moreover, granted claim 1 merely defines that the composition can be "in solution" without defining said solution, which has thus to be interpreted in a broad manner.

Finally, the respondent explained that this line of argument could not apply to the lyophilised compositions of examples 11A and 11B. This argument is not convincing. As set out under points 1.5.2-1.5.3, the Board considers that the examples 8A and 8B do not teach that any further essential component must be present in addition to the claimed components. This applies equally to these examples. Furthermore, examples 11A and 11B aim at assessing the stability of the solutions of examples 8A and 8B upon lyophilisation, as indicated by their title (see the title "Determination of botulinum toxin formulation stability [...]" in contrast to the title "Finished pharmaceutical composition" for examples 8A and 8B). Hence, the skilled person would not necessarily consider the lyophilised compositions of said stability test examples as being representative of final compositions according to the claims.

1.6 The respondent also objected that the subject-matter of granted claim 5 extended beyond the one originally disclosed and referred to the arguments developed with regard to granted claim 1. The Board considers that the same reasoning as developed above (see points 1.1 to 1.5) applies *mutatis mutandis* to the disputed amendments made in granted claim 5.

1.7 Hence the subject-matter of granted claims 1 and 5 are disclosed in the original application. The respondent did not raise the ground of opposition under Article 100(c) EPC for the remaining granted claims, the subject-matter of which are also disclosed in the original application. The Board thus comes to the conclusion that the ground of opposition under Article 100(c) EPC in combination with

Article 123(2) EPC does not prejudice the maintenance of the granted claims.

2. Remittal

2.1 Under Article 11 of the Rules of Procedure of the Boards of Appeal (RPBA) 2020 (OJ EPO 2019, A63), which applies in the present case according to Article 25(1) RPBA 2020, the Board may remit the case to the department whose decision was appealed if there are special reasons for doing so.

2.2 In the present case, the appealed decision does not address the grounds for opposition under Articles 100(a) and 100(b) EPC. As recalled in Article 12(2) RPBA 2020, the primary object of the appeal proceedings is to review the decision under appeal in a judicial manner. This principle would not be respected if the Board were to conduct a complete examination of all the grounds raised against the patent by the opponent. Consequently, under these circumstances, the Board considers that special reasons for remitting the case to the opposition division exist. The appellant had no objection against a remittal. Therefore, the Board considers it appropriate to grant the respondent's request for a remittal (Article 111(1) EPC).

Order

For these reasons it is decided that:

The decision under appeal is set aside. The case is remitted to the opposition division for further prosecution.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated