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Datasheet for the decision of 15 November 2016

Case Number: T 1907/12 - 3.3.04

Application Number: 06851349.8

Publication Number: 1926744

IPC: C07K14/33

Language of the proceedings: EN

Title of invention:
Clostridial toxin activatable Clostridial toxins

Patent Proprietor:
Allergan, Inc.

Opponent:
Merz Pharma GmbH & Co. KGaA

Headword:
Clostridial toxin/ALLERGAN

Relevant legal provisions:
EPC Art. 56, 83
EPC R. 115(2)
RPBA Art. 13(1), 15(3)

Keyword:
"Main request - requirements of the EPC met (yes)"

Decisions cited:

Catchword:

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Case Number: T 1907/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 November 2016

Appellant: (Opponent)	Merz Pharma GmbH & Co. KGaA Eckenheimer Landstrasse 100 60318 Frankfurt/Main (DE)
Representative:	Herzog, Fiesser & Partner Patentanwälte PartGmbB Dudenstrasse 46 68167 Mannheim (DE)
Respondent: (Patent Proprietor)	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 18 June 2012 rejecting the opposition filed against European patent No. 1926744 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	M. Blasi

Summary of Facts and Submissions

I. The appeal of the opponent ("appellant") lies against the decision of the opposition division rejecting the opposition filed against European patent No. 1926744 entitled "*Clostridial toxin activatable Clostridial toxins*".

Claims 1, 4, 8 and 11 as granted read (emphasis added by the board):

"1. A modified Clostridial toxin comprising a Clostridial toxin substrate cleavage site located within the di-chain loop region.

4. The modified Clostridial toxin according to Claim 1, **wherein the Clostridial toxin substrate cleavage site is derived from autocatalytic fragments of the Clostridial toxins themselves**.

8. A modified Clostridial toxin comprising a Clostridial toxin enzymatic domain, a Clostridial toxin translocation domain, a Clostridial toxin binding domain and a di-chain loop region;
wherein the di-chain loop region intervenes between the Clostridial toxin enzymatic domain and the Clostridial toxin translocation domain; and
wherein the modification comprises a Clostridial toxin substrate cleavage site located within the di-chain loop region.

11. The modified Clostridial toxin according to Claim 8, **wherein the Clostridial toxin substrate cleavage site is derived from autocatalytic fragments of the Clostridial toxins themselves**."

II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and for insufficiency of disclosure under Article 100(b) EPC. The opposition division held that the grounds of opposition cited by the opponent did not prejudice the maintenance of the patent as granted and rejected the opposition.

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

D4 US 2004/0018589

D17 Gul N. *et al.*, PloS ONE (2010), vol. 5, pages 1 to 7

D18 Declaration by Lance E. Steward, Ph.D., dated 6 October 2015

D19 Declaration by Dr. Jürgen Frevert, dated 3 June 2016

IV. With its statement of grounds of appeal, the appellant filed arguments as regards lack of inventive step of the subject-matter of claims 1 to 3, 5 to 10 and 12 to 14 of the main request underlying the decision under appeal (claims as granted), but not as regards the subject-matter of claims 4 and 11. Arguments as regards insufficiency of disclosure were also submitted.

V. With its response to the statement of grounds of appeal, the respondent requested as its main request that the appeal be dismissed, i.e. that the patent be maintained as granted, and further filed sets of claims as auxiliary requests 1 and 2 on the basis of which the

patent should be maintained if the main request was not allowable. In auxiliary request 1, the subject-matter of independent claims 1 and 7 corresponded to that of claims 4 and 11 of the main request. The remaining claims were renumbered accordingly and back-references adapted where necessary.

VI. In a further submission the appellant objected that the subject-matter of the claims lacked an essential feature, i.e. the requirement of reducing agents, and that accordingly it did not solve the problem underlying the invention (hereinafter "the reducing agent argument"). In its reply, the respondent requested that the reducing agent argument not be admitted into the proceedings.

VII. In yet a further submission the appellant submitted document D17 and further arguments as regards lack of inventive step. With its reply, the respondent submitted document D18 and requested that document D17 not be admitted into the appeal proceedings.

VIII. After the parties had been summoned to oral proceedings the appellant filed document D19 and arguments as regards insufficiency of disclosure and requested that document D17 be admitted into the appeal proceedings.

IX. Oral proceedings took place on 15 November 2016. The appellant was absent, as announced in advance in writing. During the course of the oral proceedings the respondent made its auxiliary request 1 its new main request.

Claims 1 and 7 of the new main request read:

"1. A modified Clostridial toxin comprising a Clostridial toxin substrate cleavage site located within the di-chain loop region, wherein the Clostridial toxin substrate cleavage site is derived from autocatalytic fragments of the clostridial toxins themselves.

7. A modified Clostridial toxin comprising a Clostridial toxin enzymatic domain, a Clostridial toxin translocation domain, a Clostridial toxin binding domain and a di-chain loop region;
wherein the di-chain loop region intervenes between the Clostridial toxin enzymatic domain and the Clostridial toxin translocation domain; and
wherein the modification comprises a Clostridial toxin substrate cleavage site located within the di-chain loop region, wherein the Clostridial toxin substrate cleavage site is derived from autocatalytic fragments of the clostridial toxins themselves."

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

X. The arguments of the appellant submitted in writing and relevant for the present decision may be summarised as follows:

The reducing agent argument

It was not plausible that modified Clostridial neurotoxins comprising a Clostridial toxin substrate cleavage site as described in the patent were functional in the absence of reducing agents. Claim 1 lacked an essential feature, i.e. the requirement of

reducing agents. Accordingly, said claim did not credibly solve the problem underlying the invention.

Document D17

Document D17 was *prima facie* relevant and should be admitted into the appeal proceedings. It disclosed that four variants of Botulinum neurotoxin A (BoNT/A) light chain (LC) had been generated and that none of these variants was prone to autocatalysis.

Document D19

Document D19 confirmed that the teaching of document D17 was applicable to the subject-matter of claim 1.

New main request

Sufficiency of disclosure (Article 83 EPC)

Autocatalytic fragments were described, for instance, in paragraph [0158] of the description of the patent. This paragraph indicated that peptide bonds susceptible to autocatalytic cleavage could be located in two regions of BoNT/A, with the first region comprising amino acid residues 250-267 and the second region encompassing amino acid residues 419-439 of SEQ ID NO: 1, which was the amino acid sequence of BoNT/A.

There was no evidence, either in the patent or elsewhere, with respect to the autocatalytic activation of the modified Clostridial toxins claimed. Nor did the contested patent provide sequences for them.

Thus, the person skilled in the art was not able, on the basis of the disclosure of the patent and using his common general knowledge, to generate without undue burden the claimed Clostridial neurotoxins.

Inventive step (Article 56 EPC)

Document D4 was the closest prior art. Like the patent it was concerned with the recombinant manufacture of Clostridial toxins. To this end, modified Clostridial neurotoxins were produced in which an exogenous protease cleavage site, for example that for the Factor Xa protease, was introduced into the di-chain loop region. Moreover, it was disclosed in document D4 that any other protease cleavage site could also be used, see page 2, paragraph [0017].

The subject-matter of claim 1 differed from the teaching of document D4 in that the proteolytic site to be included into the di-chain loop region was a Clostridial toxin protease cleavage site derived from autocatalytic fragments of the Clostridial toxins themselves. No particular technical effect was conferred on the modified Clostridial toxins by that modification, other than cleavability by a Clostridial toxin protease. Thus, the technical problem to be solved was the provision of a Clostridial toxin modified in that it contained an alternative protease cleavage site in its di-chain loop region.

In the absence of any working example in the patent and of any other evidence, it was not at all plausible that

the claimed modified Clostridial neurotoxins were indeed functional. Therefore the subject-matter of the claims of the new main request lacked an inventive step.

XI. The arguments of the respondent relevant for the present decision may be summarised as follows:

The reducing agent argument

The argument that there was an absolute requirement for the reduction of a Clostridial toxin in order for it to have proteolytic activity had not been made before and should not be admitted at this late stage of the proceedings. It was moreover irrelevant to the claimed subject-matter.

Document D17

Document D17 should not be admitted into the appeal proceedings. It had been stressed in the case law that evidence submitted after the expiry of the opposition period did not need to be considered, unless admitted on the grounds that the subject of the proceedings had changed. Document D17 had been cited by the appellant in the context of its submissions on autocatalytic fragments. Subject-matter directed to autocatalytic fragments was present in claims 4 and 11 as granted and had been introduced into independent claims 1 and 7 with the new main request which had originally been filed as auxiliary request 1. Accordingly, the claimed subject-matter had not changed at all.

Document D17 was also not *prima facie* relevant. It was a post-published article and as such not available as prior art against the patent in suit. Document D17 did

not look at autocatalytic cleavage of the whole BoNT/A Clostridial toxin but at cleavage of four particular variants.

Document D18

Document D18 had been submitted in response to document D17. If document D17 was admitted into the appeal proceedings, then document D18 should be admitted as well.

Document D19

Document D19 should not be admitted into the appeal proceedings.

New main request

Inventive step (Article 56 EPC)

Document D4 was the closest prior art. The claimed Clostridial toxins represented improved constructs, because they could be cleaved in an autocatalytic fashion, thus avoiding the need to add an exogenous protease. The appellant had not substantiated its argument that it was not plausible that the claimed Clostridial neurotoxins were functional. Moreover, no prior art document disclosing the autocatalytic fragments of the Clostridial toxins had been cited. Therefore the claimed solution was not obvious.

XII. The appellant requested in writing that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims filed as auxiliary request 1 together with its reply to the statement of grounds of appeal of 8 January 2013 (new main request).

Reasons for the Decision

1. The appellant did not attend the oral proceedings, although duly summoned. The board considered it expedient to conduct the scheduled oral proceedings in the appellant's absence in order to reach a final decision on this appeal, treating the appellant as relying on its written case (Rule 115(2) EPC and Article 15(3) RPBA).

The reducing agent argument

2. Article 13(1) RPBA provides that any amendment to a party's case after it has filed its statement of grounds of appeal or its reply to another party's appeal may be admitted and considered at the board's discretion. That discretion is to be exercised in view of *inter alia* the complexity of the new subject-matter admitted, the current state of the proceedings and the need for procedural economy.

3. In its statement of grounds of appeal the appellant has not raised any objections under Article 56 EPC against the subject-matter of dependent claims 4 and 11 of the main request underlying the decision under appeal (claims as granted).

4. In response to the statement of grounds of appeal, the respondent filed a set of claims as auxiliary request 1

(now the new main request) in which the subject-matter of dependent claims 4 and 11 of the main request became the subject-matter of independent claims 1 and 7. In reply, the appellant then submitted that it was not plausible that the claimed Clostridial neurotoxins were indeed functional, i.e. able to exert their proteolytic activity, in the absence of reducing agents. It concluded that the subject-matter of claim 1 of the new main request did not credibly solve the technical problem (hereinafter "the reducing agent argument").

5. The board notes that no new subject-matter was introduced by filing the new main request, as subject-matter relating to autocatalytic fragments was present in dependent claims 4 and 11 of the main request underlying the decision under appeal. This subject-matter had not been objected to in the statement of grounds of appeal (see point 3 above). The submission of the reducing agent argument at this stage of the appeal proceedings was thus not justified by the filing of the new main request by the respondent, but was an amendment of the appellant's case. Its admission for consideration was thus within the board's discretion (Article 13(1) RPBA).

6. The subject-matter of claim 1 is a modified Clostridial toxin comprising a Clostridial toxin substrate cleavage site located within the di-chain loop region, wherein the Clostridial toxin substrate cleavage site is derived from autocatalytic fragments of the Clostridial toxins themselves. The technical problem to be solved is the provision of a Clostridial toxin which is cleavable by an alternative protease (see point 21 below).

7. Claim 1 relates to the single-chain form of the Clostridial neurotoxin. Cleavage of the substrate cleavage site converts the modified toxin into the di-chain form, which is the active form of the toxin (see paragraphs [0008] and [0009] of the patent in suit, and also its Figures 4a to 6b). Accordingly, the question of whether or not the modified Clostridial neurotoxin has proteolytic activity does not arise in the assessment of whether or not the claimed subject-matter is in fact a solution to the technical problem.

8. Therefore, since the board did not consider it procedurally efficient to deal with an argument which was not pertinent to the issue to be decided, i.e. the inventiveness of the subject-matter of claim 1, it decided, in the exercise of its discretion under Article 13(1) RPBA, not to admit the reducing agent argument into the appeal proceedings.

Documents D17, D18 and D19

9. The appellant filed document D17 not with its statement of grounds of appeal but at a later stage in the appeal proceedings, in the context of its submissions on autocatalytic fragments (see section VII above). However, subject-matter relating to autocatalytic fragments was present in dependent claims 4 and 11 of the main request underlying the decision under appeal. Accordingly, the filing of document D17 was likewise considered to be an amendment of the appellant's case, to be admitted and considered at the board's discretion (see also point 2 above).

10. The appellant submitted that document D17 was *prima facie* relevant to the subject-matter of claim 1 of the new main request and should therefore be admitted. It

argued that in light of the disclosure in document D17 it was not plausible that proteolytic cleavage of a modified Botulinus neurotoxin A (BoNT/A) having one of the autocatalytic fragments in its di-chain loop region would result in an activation of BoNT/A. It was therefore not plausible that the technical problem was indeed solved.

11. Again, the board notes that the technical problem to be solved is the provision of a Clostridial toxin which is cleavable by an alternative protease (see also point 21 below). Accordingly, the question of whether or not cleavage of the modified Clostridial neurotoxin results in its activation does not arise in the assessment of inventive step of the claimed subject-matter (see also point 7 above).

12. For these reasons the board decided in the exercise of its discretion under Article 13(1) RPBA not to admit document D17. As a consequence, it likewise declined to admit into the appeal proceedings all arguments based on the teaching of document D17 as well as declarations addressing that teaching, i.e. documents D18 and D19.

New main request

13. The only issues to be dealt with by the board in relation to the claims of the new main request were whether the claimed invention was sufficiently clearly and completely disclosed for it to be carried out by a person skilled in the art and whether the claimed subject-matter involved an inventive step. The board is satisfied that the other requirements of the EPC are met.

Sufficiency of disclosure (Article 83 EPC)

14. The subject-matter of claim 1 is a modified Clostridial toxin and the only question which arises in the context of Article 83 EPC is whether the skilled person, given his common general knowledge and the teaching contained in the patent, can provide, without undue burden, toxins having the claimed structural features.

15. As also acknowledged by the appellant, the patent discloses not only the sequences of Clostridial toxins BoNT/A to BoNT/G and TeNT in Table 1 (see SEQ ID NO: 1 to 8) but also the di-chain loop regions of the Clostridial toxins in Table 8 and the autocatalytic regions of Clostridial toxins in Table 7. Moreover, in the board's view, the examples of the patent provide detailed guidance on the construction of modified Clostridial toxins, their expression and purification. In order to generate a modified Clostridial toxin it is merely required that a Clostridial toxin substrate cleavage site derived from an autocatalytic fragment be inserted within the di-chain loop region through recombinant DNA techniques.

16. Given the disclosure in the patent and in the absence of any explanation as to why the person skilled in the art was not able, on the basis of this disclosure and using his common general knowledge, to generate the modified Clostridial neurotoxin, the board is not convinced by the appellant's submission that it involved an undue burden. In the board's judgement, the manufacture of the modified Clostridial toxin is a routine matter, well within the capabilities of the average person skilled in the art of recombinant expression of proteins.

17. The board concludes that the claimed invention is sufficiently clearly and completely disclosed for it to be carried out by a person skilled in the art, and thus fulfils the requirements of Article 83 EPC.

Inventive step (Article 56 EPC)

The closest prior art

18. Both the appellant and the respondent relied on document D4 as closest prior art for the subject-matter of claim 1 of the new main request, and the board sees no reason to differ.

19. Document D4 is concerned with the recombinant manufacture of biologically active Clostridial neurotoxins. To this end, modified Clostridial neurotoxins are produced in which an exogenous protease cleavage site is introduced into the di-chain loop region, as exemplified for a Factor Xa protease site. For activation of the modified Clostridial neurotoxin after synthesis in the host cell, e.g. in *E. coli*, the neurotoxin can be purified from the host cell and then incubated with the exogenous protease. As a result, biologically active Clostridial neurotoxins are generated.

Technical problem and its solution

20. The subject-matter of claim 1 differs from the teaching of document D4 in the nature of the proteolytic site to be included in the di-chain loop region of the Clostridial neurotoxin. Thus the Clostridial toxin substrate cleavage site is derived from autocatalytic fragments of the Clostridial toxins themselves. According to paragraphs [0158] to [0168] of the patent

specification, the autocatalytic fragment can be from any Clostridial toxin and can thus be an autocatalytic fragment which is not necessarily cleaved by the modified Clostridial toxin itself but only by a Clostridial toxin of a different serotype. Accordingly, the board is not convinced that the claimed Clostridial toxins are necessarily cleavable in an autocatalytic fashion. The technical problem to be solved can thus not be formulated as the provision of improved constructs, as suggested by the respondent.

21. The appellant submitted that the problem to be solved was the provision of a Clostridial toxin modified in that it contains an alternative protease cleavage site in its di-chain loop region. However, in accordance with established jurisprudence, the problem is to be formulated on the basis of the technical effect of those features that distinguish the claimed invention from the prior art (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016, section I.D.2). The effect of the alternative protease cleavage site is that the claimed Clostridial neurotoxin is cleavable by an alternative protease. Therefore, the technical problem to be solved is the provision of a Clostridial toxin which is cleavable by an alternative protease.

22. The board is satisfied that the problem is solved by the subject-matter of claim 1.

23. The appellant submitted that it was not plausible that modified Clostridial neurotoxins comprising autocatalytic sites were indeed "functional", this

being understood to mean that they had proteolytic activity. However, the problem to be solved is not the provision of a proteolytically active neurotoxin (see point 21 above).

24. In this context, the board notes that the recombinant botulinum holotoxins of document D4 are likewise not biologically active. Only "*treatment of the recombinant holotoxins with the protease that recognizes and cuts at the engineered proteolytic site will ensure efficient cleavage of the holotoxins, and render them their biological activities*" (see document D4, paragraph [014]).

Obviousness

25. The issue as regards obviousness is whether the skilled person, faced with the technical problem defined in point 21 above, would have modified the teaching of the closest prior art document D4 - possibly in the light of other prior art teachings - so as to arrive at the claimed invention in an obvious manner.

26. Document D4 discloses (see its page 2, paragraph [0017]) that any other protease cleavage site than the Factor Xa cleavage site can be used as well. But it is silent as regards autocatalytic fragments of Clostridial toxins or their possible use as protease cleavage sites. Accordingly, the claimed solution is not obvious from the teaching of document D4 alone.

27. The appellant did not cite any prior art disclosing the autocatalytic fragments of Clostridial toxins. Nor was any argument provided as to why the skilled person, faced with the problem defined in point 21 above, would even consider replacing the Factor Xa protease site

with a Clostridial toxin substrate cleavage site derived from autocatalytic fragments of the Clostridial toxins themselves.

28. The board concludes from the above that there was nothing in the available prior art that would have motivated the skilled person to modify the teaching of document D4 to replace the Factor Xa protease site with a Clostridial toxin substrate cleavage site that is derived from autocatalytic fragments of the Clostridial toxins themselves. The skilled person would thus not have arrived in an obvious manner at the subject-matter of claim 1. The same argumentation applies to the subject-matter of independent claims 4 to 7 and 10 to 12, and to that of dependent claims 2, 3, 8 and 9 which derive their inventive step from the subject-matter of claim 1. For these reasons the claims filed as the new main request meet the requirements of Article 56 EPC.

Adaptation of the description (Article 84, second sentence, EPC) / Remittal (Article 111(1) EPC)

29. The claims of the new main request held allowable by the board no longer encompass subject-matter relating to Clostridial toxin substrate cleavage sites in general. Accordingly, the description of the patent as granted relates to subject-matter which is no longer claimed. It therefore needs to be adapted.

30. The board decided, exercising its discretion under Article 111(1) EPC, to remit the case to the opposition division for adaptation of the description and the drawings to the claims of the new main request. The party present at the oral proceedings had no objections to a remittal for that purpose.

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 in amended form, on the basis of claims 1 to 12 filed as auxiliary request 1 together with the reply of 8 January 2013 to the statement of grounds of appeal (new main request), and a description and drawings to be adapted thereto.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated