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**Datasheet for the decision  
of 6 October 2023**

**Case Number:** T 2229/19 - 3.3.08

**Application Number:** 13184864.0

**Publication Number:** 2677029

**IPC:** C12N9/52

**Language of the proceedings:** EN

**Title of invention:**

Methods for the manufacture of proteolytically processed polypeptides

**Patent Proprietor:**

Ipsen Bioinnovation Limited

**Opponent:**

Allergan, INC.

**Headword:**

Lys-C for processing BoNT A/IPSEN BIOINNOVATION

**Relevant legal provisions:**

EPC Art. 76(1)

RPBA 2020 Art. 13(2)

**Keyword:**

Prohibition of reformatio in peius (no)

Divisional application - subject-matter extends beyond content of earlier application (yes)

Amendment after summons - exceptional circumstances (no) - cogent reasons (no)

**Decisions cited:**

G 0009/92, T 1569/17, T 0494/18, T 2295/19



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Case Number: T 2229/19 - 3.3.08

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.08**  
**of 6 October 2023**

**Appellant:** Ipsen Bioinnovation Limited  
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**Decision under appeal:** **Decision of the Opposition Division of the  
European Patent Office posted on 3 June 2019  
revoking European patent No. 2677029 pursuant to  
Article 101(3) (b) EPC**

**Composition of the Board:**

**Chair** T. Sommerfeld  
**Members:** A. Schmitt  
A. Bacchin

## Summary of Facts and Submissions

- I. The appeal of the patent proprietor (appellant) lies from the decision of the opposition division to revoke European patent No. 2 677 029 (the patent).
- II. The patent was granted based on European patent application No. 13 184 864.0 (the application), which is a divisional application of European patent application No. 11 004 152.2 (the earlier application).
- III. The opposition proceedings were based on the grounds for opposition in Article 100(a) EPC, in relation to inventive step (Article 56 EPC), and in Article 100(b) and (c) EPC.
- IV. The opposition division found, *inter alia*, that the claims of the main request did not contain subject-matter that extended beyond the content of the earlier application (Article 76(1) EPC). However, the claims of the main request were considered not to comply with Article 83 EPC. Auxiliary request 1 submitted during the oral proceedings before the opposition division was not admitted into the proceedings.
- V. With the statement of grounds of appeal, the appellant maintained the sets of claims of the main request and auxiliary request 1 submitted in the opposition proceedings.

Claims 3 and 4 of the main request read as follows:

"3. Method for the manufacture of a proteolytically processed polypeptide, comprising the step of contacting:

(a) a first polypeptide, said first polypeptide being Lys-C;

with

(b) a second polypeptide, said second polypeptide being susceptible to proteolysis by said first polypeptide; wherein said contacting results in proteolytic processing of said second polypeptide into at least two cleavage products;

wherein the second polypeptide is a single-chain botulinum neurotoxin serotype A (BoNT/A) and wherein said first polypeptide hydrolyses the single-chain botulinum neurotoxin serotype A (BoNT/A) to produce a di-chain botulinum neurotoxin serotype A (BoNT/A).

4. The method according to Claim 3, wherein said single-chain botulinum neurotoxin serotype A (BoNT/A) is a naturally occurring neurotoxin, a recombinant neurotoxin, or modified neurotoxin, such as a neurotoxin lacking the native H<sub>c</sub> domain or parts thereof or derivatives with other amino acid residues replacing the neurotoxin H<sub>c</sub> domain."

Claims 3 and 4 of auxiliary request 1 are identical to claims 3 and 4 of the main request.

- VI. In the reply to the appeal, the opponent (respondent) raised, *inter alia*, objections under Article 76(1) EPC against all claims of the main request.
- VII. The board summoned the parties to oral proceedings in accordance with their requests. In a communication pursuant to Article 15(1) RPBA, the board set out its preliminary opinion that, *inter alia*, claim 4 of the main request contained subject-matter that extended beyond the content of the earlier application as filed.

VIII. In response to the board's communication, the appellant submitted sets of claims of auxiliary requests 2 and 3.

Compared to the claims of the main request, the claims of auxiliary request 2 were amended by the deletion of three dependent claims, including claim 4.

Compared to the claims of the main request, the claims of auxiliary request 3 were amended by the deletion of all dependent claims, including claim 4.

IX. In a further submission, the respondent requested that auxiliary requests 2 and 3 not be admitted and considered in the appeal proceedings pursuant to Article 13(2) RPBA.

X. The oral proceedings took place as scheduled.

XI. The appellant's arguments relevant to this decision are summarised as follows.

*Main request and auxiliary request 1  
Amendments (Article 76(1) EPC) - claims 3 and 4*

In accordance with the principle of prohibition of *reformatio in peius*, the appeal proceedings should not include a discussion of Article 76(1) EPC.

Basis for independent claim 3 of the main request and auxiliary request 1 was in paragraphs [0050] and [0051] of the earlier application; basis for the additional features of dependent claim 4 of these requests was in paragraphs [0051], [0053] and [0058] of the earlier application.

The use of the expression "[t]his method" in the first sentence of paragraph [0051] and the use and definition of the terms "first polypeptide", "BoNTHydrolase" and "second polypeptide" in paragraph [0053] and the fact that Lys-C was presented as a "first polynucleotide" in paragraph [0050] and was thus a BoNTHydrolase within the meaning of this term as used in the earlier application (i.e. any protease that hydrolyses BoNT) allowed combining the teaching in paragraph [0050] with that in paragraphs [0051] and [0058].

*Auxiliary requests 2 and 3*

*Admittance and consideration (Article 13(2) RPBA 2020)*

Auxiliary requests 2 and 3 should be considered to have been filed on time and hence admitted as the amendments in these requests only concerned the deletion of dependent claims which, under the established case law of the boards, was not an amendment within the meaning of Article 13(2) RPBA 2020 and neither raised any new issue nor changed the factual situation of the appeal or affected procedural economy. Moreover, it could not have been predicted that the board would deviate from the opposition division's decision on added matter in claim 4 in its preliminary opinion.

It had hence not been necessary to submit auxiliary requests 2 and 3 earlier in the appeal proceedings. Nor had it been necessary to submit auxiliary requests 2 and 3 during the opposition proceedings in view of the opposition division's preliminary opinion and subsequent decision that claim 4 met the requirements of Article 76(1) EPC. Addressing every objection or every permutation of objections raised by an opponent from the start of the opposition proceedings would result in an excessive number of requests. Auxiliary

requests 2 and 3 should be considered in the appeal proceedings in the interest of legal fairness.

XII. The respondent's arguments relevant to this decision are summarised as follows.

*Main request and auxiliary request 1*

*Amendments (Article 76(1) EPC) - claims 3 and 4*

The principle of prohibition of *reformatio in peius* did not apply to the case in hand. Paragraph [0050] was the only section in the earlier application that disclosed Lys-C, but it did not disclose, *inter alia*, the definition of BoNT/A in claim 4 of the main request. Paragraphs [0051], [0053] and [0058] of the earlier application could not be relied on to complement the disclosure in paragraph [0050] with missing features as any paragraph of the earlier application other than paragraph [0050], including paragraphs [0051], [0053] and [0058], related to embodiments where the proteolytic enzyme (the "first polypeptide") was endogenous BoNTHydrolase, i.e. the new proteolytically active polypeptide of the earlier application defined by reference to SEQ ID NO:1. This was evident from, for example, paragraph [0008] on page 4 and paragraph [0016] on page 7 of the earlier application.

Neither the term "BoNTHydrolase" nor the expression "first polypeptide" as used in any other paragraph of the earlier application included Lys-C. This was also clear from paragraph [0053], which provided a definition of these terms. The "*BoNTHydrolases that are obtainable from other sources*" mentioned in this paragraph were enzymes which had the same profile as the new enzyme. This did not include Lys-C.



The expression "[t]his method..." in the first sentence of paragraph [0051] did not change this fact since the content of this paragraph did not concern the method and use of Lys-C as described in paragraph [0050] but those described in all other parts of the earlier application. The appellant's argument was based purely on semantics. Claim 4 hence contained subject-matter that went beyond the disclosure of the earlier application as filed.

*Auxiliary requests 2 and 3*

*Admittance and consideration (Article 13(2) RPBA 2020)*

Auxiliary requests 2 and 3 were amendments to the appeal case. These requests could and should have been submitted earlier since the objections under Article 76(1) EPC against claim 4 had already been raised in the notice of opposition, were maintained throughout the opposition proceedings, were separately discussed during the oral proceedings before the opposition division and were maintained in the appeal proceedings. This was evident e.g. from page 8 of the notice of opposition and pages 8 to 11 of the reply to the appeal. No exceptional circumstances justified by cogent reasons were apparent why auxiliary requests 2 and 3 had not been filed earlier.

XIII. The parties' requests relevant for the decision were as follows.

The appellant requested that the decision under appeal be set aside and that the patent be maintained based on the claims of the main request or, alternatively, the claims of auxiliary request 1, both submitted with the statement of grounds of appeal, or, alternatively, the

claims of auxiliary requests 2 or 3, both submitted with the letter dated 24 August 2023.

The respondent requested that the appeal be dismissed and that auxiliary requests 1 to 3 not be admitted into the appeal proceedings.

## **Reasons for the Decision**

### *Main request*

#### *Amendments (Article 76(1) EPC) - claims 3 and 4*

1. Contrary to the appellant's arguments submitted in response to the board's communication under Article 15(1) RPBA, the principle of prohibition of *reformatio in peius* does not apply to the current case. In accordance with decision G 9/92 of the Enlarged Board of Appeal (OJ EPO 1994, 875), the principle of prohibition of *reformatio in peius* applies if the patent proprietor is the sole appellant against an interlocutory decision maintaining a patent in amended form (see Headnote I). It, however, does not apply if the patent proprietor appeals against a decision revoking a patent, as in this appeal. The board may therefore review the opposition division's decision on all requirements of the EPC, including those that the opposition division considered to be met, such as Article 76(1) EPC.
2. Claim 3 of the main request is a method of manufacture of a proteolytically processed polypeptide comprising contacting the serine endoprotease Lys-C with a single-chain botulinum neurotoxin serotype A (BoNT/A). This method results in the proteolytic processing of the single-chain BoNT/A to produce a di-chain BoNT/A.

Dependent claim 4 further defines the single-chain BoNT/A (see section V. for the full wording of the claims).

3. The opposition division came to the conclusion that a basis for claim 3 was in paragraph [0050] and a basis for claim 4 was in paragraphs [0050], [0051] and [0058] (see point 3.1.1 of the decision under appeal).
4. Paragraph [0050] of the earlier application is the only part of the earlier application that mentions the Lys-C enzyme. This was undisputed. The first sentence of this paragraph discloses that "*[t]he present invention also relates to the use of Lys-N or Lys-C and arginyl endopeptidase...*", without further specifying any purpose of this use. This sentence is therefore not a basis for the method defined in claims 3 and 4.
5. Paragraph [0050] also discloses that "*[i]n one aspect, the present invention relates to a method for the manufacture of a proteolytically processed polypeptide, comprising the step of contacting: (a) a first polypeptide, said first polypeptide being Lys-C or Lys-N, with (b) a second polypeptide, said second polypeptide being susceptible to proteolysis by said first polypeptide, wherein said contacting results in proteolytic processing of said second polypeptide into at least two cleavage products, and wherein the second polypeptide is the single chain of BoNT/A*".
6. Paragraph [0050] therefore discloses a method for proteolytically processing single-chain BoNT/A with the protease Lys-C into at least two cleavage products but does not disclose, *inter alia*, that BoNT/A is "a naturally occurring neurotoxin, a recombinant neurotoxin, or modified neurotoxin, such as a

neurotoxin lacking the native H<sub>C</sub> domain or parts thereof or derivatives with other amino acid residues replacing the neurotoxin H<sub>C</sub> domain", as required in claim 4. This was not contested by the appellant.

7. The appellant referred to paragraphs [0051] and [0058] of the earlier application as basis for these features. Paragraph [0051] discloses, *inter alia*, that "*encompassed by the term "CNT" and "BoNT" is recombinant and modified neurotoxin*". Paragraph [0058] discloses, *inter alia*, that "*[s]aid second polypeptide may be, for example, a naturally occurring neurotoxin such as BoNT/A, B, C1, D, E, F or G or a derivative thereof... . Encompassed are e.g. derivatives lacking e.g. the native neurotoxin H<sub>C</sub> domain or parts thereof or derivatives with other amino acid residues replacing the neurotoxin H<sub>C</sub> domain ...*". These paragraphs therefore disclose the additional features of claim 4.
8. However, paragraphs [0051] and [0058] relate to methods different from the proteolytic processing of single-chain BoNT/A by Lys-C disclosed in paragraph [0050]. Therefore, features from these paragraphs cannot be combined with the method described in paragraph [0050]. In fact, with the exception of paragraph [0050], each part of the earlier application on the invention concerns a proteolytically active polypeptide that is different from and unrelated to Lys-C, has a polypeptide sequence as defined in SEQ ID NO:1 or a related polypeptide sequence as defined in e.g. paragraphs [0008] and [0016], and is often referred to in the earlier application as "*the proteolytically active polypeptide of the present invention*".
9. In the context of uses for this novel polypeptide, the earlier application also employs the expressions "first

polypeptide" and "second polypeptide". Paragraph [0053] of the earlier application defines the expression "first polypeptide" in the following manner: *"The term "first polypeptide", as used herein, refers to the polypeptide of the present invention, i.e. the proteolytically active or activated polypeptide, also designated "active BoNTHydrolase". Since the active BoNTHydrolase can be obtained from the supernatant of C. botulinum, it was initially termed native BoNTHydrolase, abbreviated "nBH". However, the term "first polypeptide" and "nBH [sic] also refers to BoNTHydrolases that are obtainable from other sources."*

10. Hence, paragraph [0053] discloses that the expressions "(proteolytically active) polypeptide of the present invention", "first polypeptide", "native BoNTHydrolase" and "active BoNTHydrolase" denominate the same polypeptide, which is the novel polypeptide identified in the earlier application with reference to SEQ ID NO:1. The appellant's argument that a BoNTHydrolase was any protease that hydrolysed a BoNT does therefore not have a basis in the earlier application and cannot be accepted.
11. The appellant also asserted that Lys-C was a BoNTHydrolase within the meaning of this term as used in any other part of the earlier application since paragraph [0050] disclosed that it was a "first polypeptide" and a hydrolysed BoNT and since paragraph [0053] indicated that the terms "first polynucleotide" and "nBH" also referred to BoNTHydrolases "from other sources" (see the last cited sentence in point 9. above).
12. This interpretation is, however, not in line with the disclosure in paragraph [0053], which defines the term

"BoNTHydrolase" as referring to the novel enzyme from the bacterium *Clostridium botulinus* (*C. botulinus*) identified in the earlier application (see points 9. and 10. above and Examples 1 and 2 of the earlier application). The earlier application does not contain any unambiguous disclosure that "*BoNTHydrolases that are obtainable from other sources*", i.e. sources other than *C. botulinus*, included unrelated prior-art proteases such as Lys-C.

13. The fact that the method disclosed in paragraph [0050] also contains the expression "first polypeptide" cannot alter this assessment of the teaching in paragraph [0053] as paragraph [0050] defines this first polypeptide as "*being Lys-C or Lys-N*" (see point 5. above for the full wording of this citation). This definition in paragraph [0050] is irrelevant for the definition of the expression "first polypeptide" provided in paragraph [0053]. The latter is a generic definition which applies whenever the expression "first polynucleotide" is not otherwise defined.
  
14. Consequently, in its first three sentences (cited in point 9. above), paragraph [0053] defines the term "first polypeptide" in a manner that does not unambiguously include Lys-C. In the subsequent sentence, paragraph [0053] provides a definition of the "second polypeptide" as referring to the substrate of "*said*" first polypeptide, i.e. the first polypeptide as defined in paragraph [0053]. The subsequent paragraphs, including paragraph [0058], describe different aspects of methods using "*said*" first and second polynucleotides and therefore all relate to methods using the novel polypeptide identified in the earlier application with reference to SEQ ID NO:1 or related

proteolytically active polypeptides and a substrate of it but not Lys-C.

15. This is evident from the fact that each of these paragraphs describes a particular use or a particular "aspect" of "this" method and refers to "said" first and second polynucleotides, i.e. the ones defined in paragraph [0053]. Paragraph [0058], for example, starts with the phrase "*In another aspect, said second polypeptide...*" and hence refers back to a substrate of BoNTHydrolase but not to a substrate of Lys-C.
16. Consequently, paragraphs [0053] to [0058] concern definitions and embodiments of methods different from those described in paragraph [0050]. The incorporation of the definition of the neurotoxin described in paragraph [0058] into the method disclosed in paragraph [0050] hence creates a new technical teaching not disclosed in the earlier application as filed.
17. The appellant also argued that the definition of the neurotoxin in claim 4 that was taken from paragraph [0058] was optional ("such as") and that the remaining features were disclosed in paragraph [0051], which referred back to paragraph [0050]. This line of argument is, however, not persuasive since optional features expressed in a claim, especially in view of their interpretation with the remaining features, also need to have a basis in the patent application as originally filed and therefore also must be directly and unambiguously disclosed.
18. Moreover, despite the use of the expression "[t]his method" in the first sentence of paragraph [0051] and the fact that paragraph [0051] immediately follows paragraph [0050], the teaching in this paragraph cannot

be combined with the disclosure in paragraph [0050]. The complete first sentence of paragraph [0051] reads as follows: "*This method can be used, for example, for manufacturing proteolytically processed neurotoxin (CNT) or botulinum neurotoxin (BoNT).*" This sentence hence refers to proteolytically processing any CNT and any BoNT, whereas the method disclosed in paragraph [0050] is restricted to proteolytically processing BoNT/A (see point 5. above).

19. The disclosure in this sentence of paragraph [0051] is therefore technically inconsistent with the method described in paragraph [0050]. In view of this, paragraph [0051] can only be understood as referring to the general method of using the novel proteolytically active polypeptide of the invention disclosed in other parts of the earlier application (see e.g. paragraph [0049]) and not to the method of using Lys-C disclosed in paragraph [0050].
20. The subject-matter of at least claim 4 extends beyond the content of the earlier application as filed.
21. In view of this conclusion, the board does not need to provide reasons for whether a basis for the subject-matter of claim 3 is present in the earlier application.

*Auxiliary request 1*

*Amendments (Article 76(1) EPC)*

22. Claim 4 of auxiliary request 1 is identical to claim 4 of the main request (see section V.). Consequently, claim 4 of auxiliary request 1 contains subject-matter that extends beyond the content of the earlier



application as filed for the same reasons as claim 4 of the main request (see points 1. to 20. above).

*Auxiliary requests 2 and 3*

*Admittance and consideration (Article 13(2) RPBA 2020)*

23. In the case at hand, a summons to oral proceedings was notified after 1 January 2020, and auxiliary requests 2 and 3 were filed after the summons to oral proceedings and a communication setting out the board's preliminary opinion on the appeal had been issued. Under Article 25(3) RPBA 2020, admission of auxiliary requests 2 and 3 is thus governed by Article 13(2) RPBA 2020, which stipulates that any amendment to a party's appeal case after notification of a summons to oral proceedings must in principle not be taken into account unless there are exceptional circumstances justified with cogent reasons by the party concerned.
24. In a first line of argument, the appellant stated that since the amendments in the claims of auxiliary requests 2 and 3 only concerned the deletion of dependent claims, they were not an amendment under Article 13(2) RPBA 2020 and that the deletion of the dependent claims neither raised any new issues nor changed the factual situation of the appeal or negatively affected procedural economy.
25. The question of whether the deletion of dependent claims or an alternative from within a claim is an amendment has been answered differently by the boards (see Case Law of the Boards of Appeal of the European Patent Office, 10th edition 2022, V.A.4.2.2 d) i) and ii)). In this board's opinion, the filing of a new set of claims is to be regarded as an amendment of the

appeal case, even if only dependent claims or alternatives were deleted and its admittance is therefore subject to the board's discretion (see, for instance, T 494/18, Reasons 1.3.2; T 2295/19, in particular Reasons 3.4.4 and 3.4.5; T 1569/17, Reasons 4.3.1).

26. In the exercise of its discretion, the board may, *inter alia*, take into account the suitability of the amendment to resolve issues admissibly raised by another party in the appeal proceedings or the board (Article 13(1) RPBA). In the current case, despite the fact that the amendment introduced with auxiliary requests 2 and 3 may overcome the objection under Article 76(1) EPC, this is not the case for the objection of lack of sufficiency raised under Article 83 EPC. The opposition division had found that the invention defined in the independent claims maintained in the set of claims of auxiliary requests 2 and 3 was not sufficiently disclosed in the application (Article 83 EPC), an opinion that the board endorsed in its preliminary opinion. The deletion of the dependent claims in auxiliary requests 2 and 3 therefore did not result in claims which were clearly allowable.
  
27. In a second line of argument, the appellant argued that it had not been necessary to file auxiliary requests 2 and 3 earlier because the opposition division had considered that the main request met the requirements of Article 76(1) EPC, both in its preliminary opinion annexed to the summons to oral proceedings and in the decision under appeal. Since it could not have been predicted that the board would deviate from the opposition division's opinion, it was also not necessary to submit auxiliary requests 2 and 3 earlier in appeal.

28. This line of argument is not persuasive either. It does not support the presence of exceptional circumstances pursuant to Article 13(2) RPBA which could justify the filing of amended claims at a late stage in the proceedings. The fact that the board, in its preliminary opinion, deviated from the decision under appeal and endorsed the respondent's line of argument for an objection, which had already been raised in the notice of opposition (page 8 and the last sentence on page 9) and was maintained by the respondent in its reply to the appeal (pages 9 and 10), was a possible provisional outcome in appeal which could have been expected by all parties. The board's preliminary opinion did not contain any new, surprising facts that could justify the appellant's late reaction to the respondent's objections under Article 76(1) EPC.
29. It instead appears that the appellant, despite having reasons to file auxiliary requests 2 and 3 earlier, in opposition, did not properly address this objection. Such a reaction could also be expected as commensurate to the other party's case since the objections were straightforward and their number was reasonable. At the very latest, the appellant could have been expected to react to the respondent's reply to the appeal in which the previous objections raised under Article 76(1) EPC were maintained. It was therefore not justified to wait until after the board had issued its preliminary opinion to file these auxiliary requests.
30. Auxiliary requests 2 and 3 were therefore not admitted and considered in the appeal proceedings pursuant to Article 13(2) RPBA.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chair:



L. Malécot-Grob

T. Sommerfeld

Decision electronically authenticated