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Datasheet for the decision of 20 January 2016

Case Number: T 0313/12 - 3.3.08

Application Number: 01930035.9

Publication Number: 1281759

IPC: C12N15/16, C12P21/02, C07K14/58, C12N1/21, C12N15/09, C07K1/107

Language of the proceedings: EN

Title of invention:
METHOD OF INHIBITING THE FORMATION OF BY-PRODUCT IN THE PRODUCTION OF GENETICALLY MODIFIED POLYPEPTIDE

Patent Proprietor:
Daiichi Sankyo Company, Limited

Opponent:
Takeda GmbH

Headword:
Human atrial natriuretic peptide hANP O-acetylserine/DAIICHI

Relevant legal provisions:
EPC Art. 83, 56

Keyword:
Main Request - admissibility (yes);
Main Request - meets all requirements EPC (yes)

Decisions cited:
G 0001/03

Catchword:

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Case Number: T 0313/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 20 January 2016

Appellant: (Patent Proprietor)	Daiichi Sankyo Company, Limited 3-5-1, Nihonbashi Honcho Chuo-ku Tokyo (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Opponent)	Takeda GmbH Byk-Gulden-Strasse 2 78467 Konstanz (DE)
Representative:	Huenges, Martin Maiwald Patentanwalts GmbH Elisenhof Elisenstrasse 3 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 December 2011 revoking European patent No. 1281759 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	M. Wieser
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent no. 1 281 759 is based on European patent application no. 01 930 035.9. The patent was opposed on the grounds set forth in Articles 100(a) and (b) EPC. The opposition division considered that the Main Request and Auxiliary Requests 1-6, all filed on 26 August 2011, contravened Article 83 EPC and, accordingly, revoked the patent.

II. An appeal was lodged by the patentee (appellant). With the statement setting out its Grounds of Appeal, the appellant submitted a new Main Request and a new Auxiliary Request together with new evidence (references 1-4, renumbered as documents D14-D17). Oral proceedings were requested as an auxiliary measure.

III. In reply, the opponent (respondent) requested that the appeal be dismissed. In case that the board considered the Main Request or the Auxiliary Request to fulfil the requirements of Article 83 EPC, it requested that the case be remitted to the opposition division for further prosecution. Oral proceedings were requested as an auxiliary measure.

IV. In reply thereto, the appellant requested that the complete case be discussed and decided upon by the board in appeal proceedings.

V. The parties were summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed thereto, the parties were informed of the board's preliminary, non-binding opinion on some of the issues of the case.

In particular, the board expressed its view that the Main Request and the Auxiliary Request seemed to fulfil the requirements of Article 83 EPC. With reference to decision G 1/03 (OJ EPO 2004, page 413) and in the light of a previous communication of the opposition division, the board informed the parties that, in case that the Main Request and the Auxiliary Request were admitted into the procedure, they would be considered to meet all requirements of the EPC. Thus, a remittal to the department of first instance did not appear to be necessary.

VI. With a fax dated 9 November 2015, the respondent informed the board, without filing substantive arguments, that it would not attend the oral proceedings.

VII. In line with its preliminary, non-binding opinion, the board informed the parties that it intended to order the maintenance of the patent on the basis of the new Main Request. In view thereof, the appellant's request for oral proceedings was considered to be superfluous.

VIII. With letter of 24 November 2015, the appellant withdrew its request for oral proceedings.

IX. On 2 December 2015, the board informed the parties that the oral proceedings, scheduled for 21 January 2016, were cancelled.

X. Claim 1, the sole claim of the **Main Request**, reads as follows:

"1. A method for reducing the formation of a byproduct polypeptide containing an O-acetylserine residue in place of a serine residue by adding at least one of

histidine, methionine or glycine in an amount that inhibits biosynthesis of the amino acids added in host cells during cultivation to the medium in a method for producing a polypeptide containing a serine residue by culturing transformed *Escherichia coli*, wherein the polypeptide containing a serine residue is a human atrial natriuretic peptide."

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

D11: M.R. Larsen et al., BioTechniques, Vol. 40, No. 6, 2006, pages 790-797;

D12: S. Mukherjee et al., Science, Vol. 312, 26 May 2006, pages 1211-1214;

D13: A Database of Protein Post Translational Modifications, (The Association of Biomolecular Resource Facilities) www.abrf.org/index.cfm/dm.home?AvgMass=all

XII. The submissions of the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

Articles 123(2),(3) EPC

Claim 1 was based on granted claims 1 and 5 and contained the additional feature "*in an amount that inhibits biosynthesis of the amino acids added in host cells during cultivation*", which was directly derivable from page 8, lines 16-19 of the application as filed. The amendments resulted in a limitation of the scope of the granted claims.

Article 84 EPC

The feature added to claim 1 did not change its scope. Since any added amount of an amino acid was likely to inhibit the endogenous biosynthesis, and as costs were not a relevant technical concern, it was clear to a person skilled in the art that the addition of high amounts of amino acids was suitable.

Article 83 EPC

The presence (about 5%) of an impurity by-product polypeptide (R1) during the production of human atrial natriuretic peptide (hANP) in *E. coli* was identified in the opposed patent. As a first step, R1 was purified and a structural analysis was carried out. The results of this analysis showed R1 to have similar physical properties as hANP. R1 had the N-terminal amino acid sequence of hANP and a molecular weight (MW) determined by mass spectrometry (MS) of 3122 which was greater by +42 than the MW of hANP (3080). Evidence on file (documents D11 and D13) showed that MS was a standard technique for determining post-translational modifications of proteins and disclosed the mass shift of proteins resulting from these modifications. The +42 mass shift and the fact that the modification reaction occurred in cells led to the conclusion that the modification was an acetyl group (O-acetylation). The acetylation site could only be serine (Ser), arginine (Arg) or tyrosine (Tyr).

hANP had only one (C-terminal) Tyr which was experimentally shown not to be acetylated. The Arg residues were also shown not to be acetylated because R1 was properly cleaved with a protease specifically recognising Arg, namely trypsin. It was known in the

art that whilst unmodified Arg was specifically cleaved with trypsin, modified Arg could not be cleaved. Thus, a skilled person would have recognized from the disclosure of the patent that Arg residues in R1 were not modified because the digestion pattern of R1 by trypsin was identical to that of hANP.

Modifications on lysine (Lys) residues resulting in a +42 mass shift, i.e. Lys trimethylation or acetylation (documents D11 and D13), were excluded because there was no Lys in the amino acid sequence of hANP. The carbamylation of Lys or Arg residues or of the N-terminal of the peptide resulted in a +43 MW change and not in the +42 mass shift. Thus, all possible alternative modifications, mentioned in the decision under appeal, did in fact not exist. There was no reason to doubt the presence of an O-acetylserine residue at a Ser residue in R1, as required by claim 1 of the Main Request.

As regards the amount of amino acids to be supplemented to the medium, the indication of specific calculations was not a prerequisite for a person skilled in the art. A skilled person in the field of microbiology would have found it straightforward to add a high amount of amino acids. Moreover, Example 3 of the opposed patent gave detailed information how to provide amino acids and in which amount.

XIII. The respondent did not file new substantive arguments, but referred to previous submissions made before the opposition division. With regard to Article 83 EPC, it referred to the Notice of opposition (pages 19-20), the submissions of 9 September 2011 (pages 5-8) and the submissions made at the oral proceedings on 9 November 2011 as reflected by the minutes (item 3.7).

Also with regard to the requirements of Articles 54 and 56 EPC, the respondent referred to these earlier submissions (pages 5-19, Notice of opposition; pages 1-5, 8-9, submissions of 9 September 2011). The arguments presented there with respect to insufficiency of disclosure, lack of novelty and lack of inventive step, applied also to the present Main Request, which did not fulfil the requirements of Articles 83, 54 and 56 EPC.

XIV. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the Main Request or the Auxiliary Request, both filed with the statement setting out the Grounds of Appeal.

XV. The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

Cancellation of the scheduled oral proceedings

1. In reply to the board's communication pursuant to Article 15(1) RPBA, the respondent did not reply in substance, but, with a fax dated 9 November 2015, merely informed the board that it would not attend the scheduled oral proceedings (cf. point VI *supra*).

2. By its decision not to attend the scheduled oral proceedings and not to file substantive arguments, the respondent has chosen not to make use of the opportunity to comment on the board's opinion, either in written form or orally at oral proceedings. This was done although the board's preliminary opinion was

against the respondent since the board was of the preliminary, non-binding opinion that the Main Request and Auxiliary Request fulfilled the requirements of Article 83 EPC and of all other requirements of the EPC (cf. page 7, points 19 and 22 of the board's communication). Moreover, in this communication, the board also informed the parties of its intention not to remit the case to the department of first instance for further prosecution (cf. page 8, point 23 of the board's communication).

3. In the light thereof and since also the appellant withdrew its request for oral proceedings, the board cancelled the oral proceedings scheduled for 21 January 2016.

Main Request

4. The Main Request filed in appeal proceedings is based on Auxiliary Request 4 filed on 26 August 2011 prior to the oral proceedings before the opposition division. Claim 1, the sole claim of the Main Request, results from a combination of claims 1 and 2 of this former Auxiliary Request. The Main Request is admitted into the procedure.

Articles 123(2),(3) EPC

5. Claim 1 results from a combination of claims 1 and 5 as granted with the additional feature "*in an amount that inhibits biosynthesis of the amino acids added in host cells during cultivation*", which is found on page 8, lines 16-19 of the application as filed. The respondent has not raised any objection under these articles and the board sees no reason to raise any of its own.

Article 84 EPC

6. The decision of the opposition division regarding clarity of the added feature has not been contested by the respondent (cf. page 2, point II of its reply to the appellant's Grounds of Appeal). The Main Request fulfils the requirements of Article 84 EPC.

Article 83 EPC

7. The "*polypeptide containing a serine residue*" has been limited in claim 1 to "*a human atrial natriuretic peptide*" (hANP), the specific polypeptide exemplified in the patent. There is no lysine residue ("*Lys*") in the amino acid sequence of the hANP (cf. SEQ ID NO: 1 of the patent). The limitation of the claimed subject matter to hANP excludes the presence of any by-product polypeptide with modifications in a Lys residue, such as Lys acetylation and N-trimethylation of lysine (cf. document D13).

8. According to the "*Identification of the impurity R1*" on page 3, paragraphs [0014] to [0016] of the patent, "*R1 has a molecular weight greater by **42** than that of hANP*" (determined by mass spectrometry (MS) and amino acid sequencing). There is no experimental or other technical evidence on file that this value could be wrong or that could support a possible mass shift, for instance to +43, as referred to by the respondent and by the opposition division in the decision under appeal (cf. page 3, last paragraph of the appealed decision).

9. In view of the evidence on file (cf. documents D12 and D13), there is no reason for the board to question that the "*acetylation*" disclosed in the patent is the sole modification of the R1 impurity of hANP (cf. page 3,

paragraph [0015]). Paragraph [0016] states that, "*as for the acetylation site, the amino acid sequence of hANP implies the possibility of modification at serine, arginine and tyrosine residues*". In the same paragraph, the modification of the sole (C-terminal) tyrosine in the hANP is clearly excluded, so that the only residues which remain to be considered are hANP serine and arginine.

10. A possible modification (acetylation) of an arginine residue is excluded by the results obtained in a cleavage test carried out with a protease (trypsin) specifically recognizing this amino acid residue (cf. page 3, paragraph [0016], lines 41-42 of the patent). According to the opposition division, the trypsin cleavage test provides only unreliable "*inconclusive data*" (cf. page 4, fourth paragraph of the decision under appeal). However, there is no evidence on file, showing that the assumption made in the patent is wrong and that the actual modification of the impurity R1 of hANP is indeed an acetylation of an arginine residue and not of a serine.

11. Even when assuming that the trypsin cleavage test is not absolutely reliable, the board notes that the patent also refers to mass spectrometry and amino acid sequencing and does not exclude other methods known in the art for measuring and determining the presence of an O-acetyl serine in the hANP polypeptide, such as the MS/MS method.

12. Thus, the board decides that, in view of the limitation of the subject-matter of the Main Request to hANP as "*the polypeptide containing a serine residue*", the objection under Article 83 EPC, raised in the decision under appeal is overcome.

13. As regards the objection concerning the determination of the amount of the amino acid to be added (cf. page 3, point 1 of the decision under appeal), the board, in view of the disclosure in Example 3 of the patent and of appellant's arguments put forward in its Grounds of Appeal (cf. point XII *supra*), does not see any reason to deviate from the decision of the opposition division. The less so since the claimed method does not define any particular degree of reduction of the formation of the O-acetyl serine by-product.

14. Thus, the invention according to Main Request is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art and, thus, meets the requirements of Article 83 EPC.

Remittal to the Opposition Division (Article 111(1) EPC)

15. The decision under appeal is concerned only with the requirements of Articles 84 and 83 EPC.

16. The respondent, at the onset of the appeal procedure, has requested, that, in case that the board considered the Main Request or the Auxiliary Request to fulfil the requirements of Article 83 EPC, the case be remitted to the opposition division for further prosecution (cf. point III *supra*).

17. Remittal to the department of first instance is at the boards discretion and there is no absolute right for a party to have its case considered by two instances (cf. "Case Law of the Boards of Appeal of the EPO", 7th edition 2013, IV.E.7.6, page 1028).

18. In the present case the opposition division has expressed its preliminary opinion on the issues of novelty and inventive step (Articles 54 and 56 EPC) in a detailed communication issued on 20 May 2011 and sent with the summons to oral proceedings. Although the claim requests considered in this communication differed from the Main Request, the considerations made apply also to the Main Request.

In said communication, the opposition division acknowledged novelty of the subject-matter of all claims then on file, but considered all of them not to fulfil the requirements of Article 56 EPC. Although the opposition division, in the light of the disclosures in the prior art and of the common general knowledge of a skilled person, was of the preliminary opinion that the claimed method was not obvious, it came to the preliminary conclusion that "*there is no sufficient evidence that the problem posed, i.e. prevent formation of a by-product polypeptide containing an O-acetyl serine residue, has actually been solved*" (cf. page 10, point 12.1.3 and page 11, point 12.2.3 of the communication of the opposition division issued on 20 May 2011).

19. In the communication pursuant to Article 15(1) RPBA, the board informed the parties that, considering the limited scope of the newly filed Main and Auxiliary Request, in case of a positive decision on the issue of sufficiency, "*a remittal to the department of first instance does not appear to be necessary*" (cf. page 8, point 23 of the board's communication).

20. The appellant did not submit any substantive reply to this communication, in detail, it did not comment on the boards view that a remittal was not required.

21. In the light of this situation the board rejects respondent's request for remittal according to Article 111(1) EPC and decides to examine the complete case itself.

Article 100(a) EPC (Articles 54 and 56 EPC)

22. The opposition division already mentioned in its communication issued on 20 May 2011 that it considered the subject-matter of the claim of the Main Request to be novel. Also the board, in its communication, has expressed its preliminary opinion that the requirements of Article 54 EPC are met (cf. point 22 of the communication).

23. In the appeal procedure the respondent has only referred to its submissions filed at first instance proceedings and did not reply to the board's communication.

24. The subject-matter of the sole claim of the Main Request is not disclosed in any of the prior art documents on file. The requirements of Article 54 EPC are met.

25. As already mentioned in point 21 of the board's communication, when the desired effect of the claimed method, namely "*reducing the formation of a byproduct polypeptide containing an O-acetylserine residue in place of a serine residue*", is expressed in the claim, the achievement of this effect is a question of Article 83 EPC (cf. decision G 1/03, OJ EPO 2004, page 413, point 2.5.2 of the Reasons) and not, as considered by the opposition division, a question of Article 56 EPC.

26. This issue has been answered by the board in the favour of the appellant in points 8 to 15 above. The Opposition Division in its communication of 20 May 2011 has already taken the view that the claimed method cannot be derived in an obvious way from the disclosure in the prior art documents on file. This statement has not been put into question by the respondent in the appeal procedure. The board sees no reason to do so and hence finds that the Main Request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the Main Request (claim 1) filed with the statement setting out the Grounds of Appeal and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated