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**Datasheet for the decision
of 30 October 2019**

Case Number: T 0776/16 - 3.3.08

Application Number: 07717002.5

Publication Number: 1984517

IPC: C12P21/00

Language of the proceedings: EN

Title of invention:

METHODS FOR MODULATING MANNOSE CONTENT OF RECOMBINANT PROTEINS

Patent Proprietor:

Amgen Inc.

Opponent:

Franke, Andreas

Headword:

Reducing mannose content/AMGEN

Relevant legal provisions:

EPC Art. 123(2)

Keyword:

Main request - extension beyond the content of the application as filed (yes)

Admission of auxiliary requests I, II, IIa, III and IIIa into the proceedings (yes)

All auxiliary requests - extension beyond the content of the application as filed (yes)

Decisions cited:

T 0002/81, T 1511/07

Catchword:



Beschwerdekammern

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Chambres de recours

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Case Number: T 0776/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 30 October 2019

Appellant: Amgen Inc.
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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
14 January 2016 concerning maintenance of the
European Patent No. 1984517 in amended form.**

Composition of the Board:

Chairman B. Stolz
Members: M. R. Vega Laso
D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 984 517 with the title "Methods for modulating mannose content of recombinant proteins" was granted from the European application No. 07717002.5 which was filed under the Patent Cooperation Treaty and published as WO 2007/087384 (in the following "the application as filed").

II. Claims 1 and 2 of the patent as granted read as follows:

"1. A method of reducing the high-mannose content of recombinantly produced glycoprotein so that less than about 10% of the glycoproteins in the composition have more than 4 mannose residues per N-linked oligosaccharide, comprising culturing a mammalian host-cell, which expresses the recombinant glycoprotein, for about 5 to 14 days in a culture medium having an osmolality of about 250 mOsm/Kg to about 600 mOsm/Kg, the culture medium comprising betaine at a concentration of about 20 mM to about 30 mM, potassium at a concentration of about 10 mM to about 70 mM, and sodium at a concentration of about 50 mM to about 200 mM.

2. A method of reducing the high-mannose content of recombinantly produced antibody, or an antigen-binding fragment thereof, so that less than about 10% of the glycoproteins in the composition have more than 4 mannose residues per N-linked oligosaccharide, comprising culturing a mammalian host-cell, which expresses the recombinant antibody or antigen-binding fragment thereof, in a culture medium having an osmolality of about 250 mOsm/Kg to about 600 mOsm/Kg,

the culture medium comprising betaine at a concentration of about 20 mM to about 30 mM, potassium at a concentration of about 10 mM to about 70 mM, and sodium at a concentration of about 50 mM to about 200 mM."

Dependent claims 3 to 11 are directed to embodiments of the method of claim 1 and/or claim 2.

- III. The patent was opposed on the grounds for opposition of Article 100(a) in conjunction with Article 56, 100(b) and 100(c) EPC.
- IV. In an interlocutory decision posted on 14 January 2016, an opposition division found that the subject-matter of the claims of the patent as granted (main request) and of the auxiliary request I to III then on file extended beyond the content of the application as filed (Articles 100(c) and 123(2) EPC). While the set of claims according to the auxiliary request IV filed at the oral proceedings was not admitted into the proceedings, the amended claims 1 to 4 according to the auxiliary request V filed during the oral proceedings and a description adapted thereto were found to meet the requirements of the EPC. Accordingly, the opposition division decided that the patent could be maintained on this basis.
- V. The patent proprietor (appellant) filed an appeal against the interlocutory decision. It maintained the claims of the patent as granted as its main request and submitted together with its statement of grounds of appeal four sets of claims as new auxiliary requests I to IV. As a subsidiary request, it was requested that oral proceedings be held if the board considered taking any decision adverse to the appellant.

- VI. Claim 1 of the **auxiliary request I** differs from claim 1 of the patent as granted (see section II above) in that the mammalian host cell is cultured "*at a temperature of 31°C to 38°C*".
- VII. Claims 1 and 2 of the **auxiliary request II** differ from the corresponding claims of the patent as granted in that they specify that the culture medium has "*... an osmolality of about 250 mOsm/Kg to about 500 mOsm/Kg ...*", and comprises "*... potassium at a concentration of about 10 mM to about 50 mM, and sodium at a concentration of about 50 mM to about 100 mM.*" (emphasis added by the board).
- VIII. In claims 1 and 2 of the **auxiliary request III** the amendments introduced in the corresponding claims of both the auxiliary request I and II are combined.
- IX. The set of claims according to the **auxiliary request IV** differs from the claims of the patent as granted in that claim 1 has been omitted and the remaining claims have been re-numbered as claims 1 to 10.
- X. The opponent (respondent) was invited to submit observations on the statement of grounds of appeal. However, none were received.
- XI. The parties were summoned to oral proceedings before the board. In a communication sent in preparation of the oral proceedings, the board expressed a provisional opinion on some procedural and substantive issues, in particular issues relating to Article 123(2) EPC.
- XII. In response to the summons, the respondent made observations on the admission of the auxiliary

requests I to III, and informed the board that it would not be represented at the oral proceedings.

- XIII. The appellant replied to the board's communication and filed two additional sets of claims as **auxiliary requests IIa and IIIa**. These sets of claims are identical to those of, respectively, auxiliary request II and III, except that in claims 1 and 2 the word "about" has been omitted for the upper limit of the ranges for potassium and sodium concentration.
- XIV. Oral proceedings were held on 30 October 2018 in the absence of the respondent.
- XV. The submissions made by the appellant were essentially as follows:

Main request (patent as granted) - Article 100(c) EPC

The opposition division incorrectly found that the ground for opposition of Article 100(c) EPC prejudiced the maintenance of the patent as granted, because the combination of ranges for the osmolality and the betaine, potassium and sodium concentration specified in claim 1 had no basis in the application as filed.

It was disclosed in paragraph [0011] of the application as filed that the desired low-mannose content could be achieved by maintaining the cell culture environment at a low osmolality. The paragraph then went on to list several osmolality ranges, which served as a basis for the range in claim 1, as acknowledged by the opposition division. In the next paragraph disclosing sodium and potassium ranges, it was stated that those concentration ranges were a means for achieving the "foregoing osmolality ranges". The osmolality was also

explicitly mentioned in the last sentence of the paragraph. There could be no doubt that the advantageous sodium and potassium ranges were disclosed in a manner *clearly linked* to the osmolality described in paragraph [0011], namely as a specific means for achieving such an osmolality.

Furthermore, paragraph [0015] explicitly disclosed the betaine range specified in claim 1. Betaine was described as an *osmoprotectant* and introduced as *necessary* to maintain the osmolality at a desired level. Thus, the betaine concentration was also clearly linked to the desired osmolality. The claimed cultivation range was disclosed in paragraph [0016] and in dependent claim 16, which linked it to the previously mentioned osmolality and ion concentration ranges.

Similar disclosure could be found in paragraphs [0091] and [0093] for osmolality and betaine concentration. Furthermore, paragraph [0097] disclosed the potassium concentration specified in claim 1, and in paragraph [0098] it was mentioned that the medium may *further* include the desired sodium concentration. Thus, both ion concentrations were disclosed together, and in paragraph [0098] it was stated that those concentrations were used to control factors that affect osmolality.

Taking those sections of the description together, there was a clearly disclosed link between the desired osmolality and the factors of potassium, sodium, and betaine (in their respective concentrations) which should be used to achieve and maintain the desired osmolality, along with the cultivation time. Accordingly, contrary to the finding in the decision

under appeal, claim 1 of the patent as granted did not include any added matter.

Admission of the auxiliary requests I to IV, IIa and IIIa into the proceedings

The auxiliary requests I to IV should be admitted into the proceedings. In the summons to oral proceedings, the opposition division had **not** seen any added-matter problem with respect to the combination of ranges in claim 1 as granted. Hence, there had been no reason for filing amended requests. The opposition division's change of mind during the oral proceedings had taken the patent proprietor by surprise.

*Auxiliary requests I to IV, IIa and IIIa -
Article 123(2) EPC*

The arguments put forward in connection with the main request applied also to the auxiliary requests. In particular, in auxiliary requests II and III the concentration ranges had been amended to recite ranges explicitly disclosed in the application as filed, without the need for combination along the rules of decision T 2/81 (OJ EPO 1982, 394). Thus, at least the auxiliary requests II and III should be regarded as finding explicit support in the application as filed.

XVI. The submissions by the respondent were as follows:

Admission of the auxiliary requests I to III into the proceedings

The auxiliary requests I to III filed together with the statement of grounds of appeal should not be admitted into the proceedings because they could have been

submitted in opposition proceedings. The amendments introduced into the claims according to those requests were an attempt to overcome objections under Article 123(2) EPC which had been raised already in the notice of opposition.

- XVII. The appellant (patent proprietor) requested that the decision under appeal be set aside, and that the patent be maintained as granted (main request), or alternatively that the patent be maintained upon the basis of one of auxiliary requests I to IV, all filed under cover of a letter dated 13 May 2016, or upon the basis of one of Auxiliary Requests IIa or IIIa, both filed under cover of a letter dated 30 September 2019.
- XVIII. The respondent (opponent) requested in writing that auxiliary requests I to III not be admitted into the proceedings and that the appeal be dismissed.

Reasons for the Decision

Main request (patent as granted) - Article 100(c) EPC

1. In the decision under appeal, the opposition division held that, although the individual ranges specified in claim 1 - including those resulting from new combinations of disclosed end-points - had a basis in the application as filed, the combination of all the specific ranges in one single method as defined in claim 1 had no basis in the application as filed. In their view, there was also no basis for the combination of all the specific ranges with the feature that the mammalian host cell is cultured for about 5 to 14 days (see section 4.5 of the decision).

2. The appellant contested this finding. As basis for the subject-matter of claim 1, it referred to paragraphs [0011], [0012], [0015], [0016], [0090], [0091], [0093], [0097] and [0098] as well as to claims 4 and 16 of the application as filed.

3. It is consistent jurisprudence of the Boards of Appeal that, when assessing whether or not an amended patent application extends beyond the content of the application as filed (Article 123(2) EPC), the content of the application as filed must not be considered to be a "reservoir" from which features pertaining to separate embodiments of the invention can be combined in order to artificially create a new embodiment. In particular, the Boards hold that, although the selection of explicitly disclosed values defining different (sub)ranges in order to form a new (sub)range might be acceptable under Article 123(2) EPC when the ranges belong to the same list, the combination of an individual range from a list with another individual range emerging from a second list of ranges and relating to a different feature has no basis in the application as filed, **unless** there is a clear pointer to such a combination (see *inter alia* decision T 1511/07 of 31 July 2009). The same applies when assessing whether the subject-matter of a patent extends beyond the content of the application as filed (Article 100(c) EPC).

4. In the present case, the range specified in claim 1 for each of the potassium and sodium concentrations in the culture medium is formed by combining two different ranges disclosed in paragraph [0012] of the application as filed. The passage on page 4, lines 1 to 4, mentions a broader range ("about **70 mM or less**" for potassium and "about **200 mM or less**" for sodium) and a single

narrower range ("about **10 mM** to about 50 mM" for potassium and "about **50 mM** to about 100 mM" for sodium). In claim 1 of the patent as granted, the lower end-point of the narrower ranges is combined with the upper end-point of the broader ranges as follows:
"... potassium at a concentration of about 10 mM to about 70 mM, and sodium at a concentration of about 50 mM to about 200 mM".

5. As regards the osmolality, the upper and lower end-points of the new range specified in claim 1 (*"... of about 250 mOsm/Kg to about 600 mOsm/Kg ..."*) are selected from a rather long list of possible ranges (see paragraph [0011], last four lines; *"... in a medium having an osmolality of about **600** mOsm/Kg or less (e.g., between a range of about 200 and 600 mOsm/Kg, e.g., about **250** and 550 mOsm/Kg, about 250 and 500 mOsm/Kg, about 250 and 450 mOsm/Kg, about 250 and 400 mOsm/Kg, about 250 and 380 mOsm/Kg, or about 250 and 350 mOsm/Kg)"*).
6. Finally, the range specified in claim 1 for the betaine concentration is selected among three different ranges explicitly disclosed in paragraph [0015] of the application as filed (*"... In a particular embodiment, the osmoprotectant (e.g., betaine) is present at a concentration of about 20 mM or greater in the cell culture medium. In particular embodiments, the osmoprotectant (e.g., betaine) is present at a concentration of about 1 mM to about 100 mM or at **about 20 mM to about 30 mM"**)*).
7. The appellant contended that the osmolality and betaine ranges specified in claim 1 of the patent as granted are apparent from, respectively, claims 4 and 16 of the application as filed. However, there is no link

whatsoever between the embodiments of claims 4 and 16. Both claims refer - directly or indirectly - to the methods of claims 1 to 3 and thus are directed to two independent embodiments of those methods.

8. Even though it is stated in paragraph [0016] of the application as filed that additional cell culture parameters like temperature and duration of the cell culture "*... may be controlled, either alone or in combination with one or more of the parameters described herein ...*", there is no clear pointer in either paragraphs [0011], [0012], [0015] and [0016] or elsewhere in the chapter under the heading "Summary of the invention" to the particular combination of ranges for the different parameters as specified in claim 1. Contrary to the appellant's view, the fact that the potassium and sodium concentrations have an influence on the osmolality, and that in the application as filed betaine is described as an osmoprotectant, only indicates that there is a technical relationship between the four parameters, but does not provide a clear pointer to a combination of the specific ranges for those parameters as specified in claim 1.

9. As the appellant contended, an osmolality range of about 250 mOsm/Kg to about 600 mOsm/Kg as specified in claim 1 is explicitly disclosed in paragraph [0090] of the application as filed, and the range for the betaine concentration specified in claim 1 is disclosed in paragraph [0093] as the more preferred range among the three specified ranges. However, there is no explicit basis in any of the paragraphs [0091], [0093], [0097] and [0098] for the range for each of the potassium and sodium concentrations as recited in claim 1, which can only be formed by combining the end-points of two different ranges (see last two lines of paragraphs

[0097] and [0098] for the potassium and sodium concentration, respectively). Like the disclosure in the paragraphs in the chapter "Summary of the Invention" to which the appellant referred, the disclosure in paragraphs [0090], [0091], [0093], [0097] and [0098] does not provide a clear pointer to the particular combination of ranges for the different parameters specified in claim 1. Moreover, the duration of the cell culture specified in claim 1 ("*for about 5 to 14 days*") cannot be derived from any of these paragraphs.

10. In view of the above, the board considers the opposition division's finding that the subject-matter of claim 1 extends beyond the content of the application as filed, to be correct. The same applies as regards claim 2 which specifies the same ranges as claim 1 for each of the betaine, potassium and sodium concentrations and the osmolality.
11. Hence, the opposition ground of Article 100(c) EPC prejudices the maintenance of the patent as granted.

Admission of the auxiliary requests I to III, IIa and IIIa into the proceedings (Article 12(4) RPBA)

12. The amendments introduced into the claims according to the auxiliary requests I to III filed together with the statement of grounds of appeal represent new attempts to remedy the deficiencies under Article 123(2) EPC which led to the refusal of the main request in opposition proceedings. Auxiliary request IV in appeal proceedings is identical to the auxiliary request II underlying the decision under appeal.

13. The board accepts that, under the circumstances of the present case, i.e. the favourable provisional opinion expressed by the opposition division as regards the compliance of claims 1 and 2 with Article 123(2) EPC (section 3.3 of the summons to oral proceedings dated 1 June 2015), and the surprising adverse finding in this respect at the oral proceedings (see sections 4.4 and 4.5 of the decision under appeal), the non-admission of the new auxiliary requests would unduly curtail the appellant's right to defend its patent. Since the requests were filed together with the statement of grounds of appeal, i.e. at the earliest possible point of time in appeal proceedings, the board decides to admit and consider them.

14. Auxiliary requests IIa and IIIa, which differ from, respectively, the auxiliary requests II and III in that the word "about" has been omitted from the upper limit of the ranges for potassium and sodium concentration, were filed in reply to a new objection under Article 84 EPC raised by the board in its communication in preparation of the oral proceedings. Since they have been submitted in due time and overcome the objection raised by the board, the auxiliary requests IIa and IIIa are admitted into the proceedings.

Auxiliary requests I to IV, IIa and IIIa - Article 123(2) EPC

15. Amended claim 1 of the auxiliary request I differs from claim 1 of the patent as granted in that it includes a further feature specifying a temperature range ("31°C to 38°C") for the culture. Claim 2 is identical to the corresponding claim of the patent as granted.

16. As stated in connection with the main request (see paragraphs 4 to 9 above), also claims 1 and 2 of

auxiliary request I are directed to new embodiments defined by a combination of ranges and further features for which the application as filed does not provide a clear pointer. For this reason and in accordance with the jurisprudence of the Boards of Appeal, their subject-matter is regarded as extending beyond the content of the application as filed. Consequently, Article 123(2) EPC is contravened.

17. In claims 1 and 2 of auxiliary requests II and IIa, the ranges for the potassium and sodium concentration as well as the range for osmolality have been amended (see section VII above). While the amended ranges are explicitly disclosed in the application as filed - rather than resulting from the combination of lower and upper end-points of different ranges disclosed, as is the case for claims 1 and 2 of the patent as granted -, there is no pointer whatsoever in the application as filed to a method defined by the particular combination of ranges recited in claims 1 and 2 of the auxiliary requests II and IIa. Hence, since the claimed subject-matter extends beyond the content of the application as filed, the amendments offend against Article 123(2) EPC.
18. The amendments introduced into claim 1 of auxiliary request III combine those introduced into the corresponding claim of the auxiliary requests I and II. Claim 2 is identical to the claim 2 of auxiliary request II. For the reasons given in paragraph 17 above, also the amendments introduced into claims 1 and 2 of auxiliary request III offend against Article 123(2) EPC. The same applies *mutatis mutandis* to auxiliary request IIIa.

19. The present auxiliary request IV is identical to the auxiliary request II underlying the decision under appeal. The opposition division found that the combination of ranges specified in claim 1 was objectionable under Article 123(2) EPC (see section 5.3 of the decision under appeal). The board shares this view. Claim 1 of auxiliary request IV is identical to claim 2 of the patent as granted. Hence, the reasons given in paragraphs 4 to 10 above in connection with the main request apply equally to the auxiliary request IV.

Conclusion

20. Since the opposition ground of Article 100(c) EPC prejudices the maintenance of the patent as granted, and the amendments introduced into the claims according to the auxiliary requests I to IV and IIa to IIIa, contravene Article 123(2) EPC, the decision under appeal cannot be set aside.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



L. Malécot-Grob

B. Stolz

Decision electronically authenticated