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Datasheet for the decision of 6 July 2023

Case Number: T 0385/21 - 3.3.04

Application Number: 12713737.0

Publication Number: 2697251

IPC: C07K14/435, C12N5/00, C07K14/43

Language of the proceedings: EN

Title of invention:
A method for controlling the main complex N-glycan structures and the acidic variants and variability in bioprocesses producing recombinant proteins

Patent Proprietor:
LEK Pharmaceuticals d.d.

Opponents:
Patentanwälte Isenbruck Bösl Hörschler PartG mbB
Hoffman Eitle Patent- und Rechtsanwälte Partnerschaftsgesellschaft mbB

Headword:
Galactosylation method/LEK

Relevant legal provisions:
EPC Art. 54

Keyword:
Novelty - (no)

Decisions cited:
T 0304/08, T 1931/14

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

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Case Number: T 0385/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 July 2023

Appellant I: (Opponent 1)	Patentanwälte Isenbruck Bösl Hörschler PartG mbB Prinzregentenstrasse 68 81675 München (DE)
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Respondent: (Patent Proprietor)	LEK Pharmaceuticals d.d. Verovskova 57 1526 Ljubljana (SI)
Representative:	Rückerl, Florian Dehmel & Bettenhausen Patentanwälte PartmbB Herzogspitalstraße 11 80331 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 16 March 2021 rejecting the opposition filed against European patent No. 2697251 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	D. Luis Alves
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 2 697 251, entitled "A method for controlling the main complex N-glycan structures and the acidic variants and variability in bioprocesses producing recombinant proteins", was granted on the basis of European patent application No. 12 713 737.0, filed as an international application published as WO 2012/140138.

II. Two parties filed oppositions, invoking Article 100(a) EPC, in combination with Articles 54 and 56 EPC, and Article 100(b) and (c) EPC, as grounds for opposition.

The opposition division decided to reject the oppositions. Both opponent 1 (appellant I) and opponent 2 (appellant II) appealed this decision.

III. With the reply to the appeals, the patent proprietor (respondent) submitted arguments and claim sets of auxiliary requests 1 to 6, auxiliary requests 1 to 3 being identical to those filed in opposition proceedings.

IV. The board summoned the parties to oral proceedings. In a communication pursuant to Article 15(1) RPBA 2020, it informed them of its preliminary opinion on some of the substantive and legal matters concerning the appeal.

V. Oral proceedings were held by videoconference. At the oral proceedings the respondent maintained its main request and auxiliary request 1, made auxiliary request 5 its auxiliary request 2, filed a new set of

claims as auxiliary request 3, and withdrew all other claim requests.

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

VI. Claim 1 of the **main request** (patent as granted) reads as follows.

"1. A method of controlling quality and quantity of posttranslational modification of a recombinantly produced polypeptide/protein (glycoprotein), wherein the posttranslational modification is selected from bG0 structures and bG1 structures, and wherein the polypeptide/protein (glycoprotein) production is in eukaryotic host cells, the method comprising the following steps:
a) cultivating the eukaryotic cells in a suitable medium under conditions which allow the expression of the polypeptide/protein, wherein the content of the dissolved CO_2 (pCO_2) in the medium is at a first value during the initial growth phase of the eukaryotic cells, allowing the eukaryotic cells to grow, and
b) increasing or decreasing the content of the dissolved CO_2 (pCO_2) in the medium during the production phase of the eukaryotic cells to a second value."

Claim 1 of **auxiliary request 1** reads as claim 1 of the main request except for step b), which reads as follows.

"b) increasing the content of the dissolved CO_2 (pCO_2) in the medium during the production phase of the eukaryotic cells to a second value to increase the amount of bG0 structures and to decrease the amount of

bG1 structures, relative to the amounts obtained by a method with no pCO_2 regulation, or decreasing the content of the dissolved CO_2 (pCO_2) in the medium during the production phase of the eukaryotic cells to a second value to decrease the amount of bG0 structures and to increase the amount of bG1 structures, relative to the amounts obtained by a method with no pCO_2 regulation."

Claim 1 of **auxiliary request 2** reads as claim 1 of auxiliary request 1 except for step b), which reads as follows (differences highlighted by the board, using underlining for additions and strike-through for deletions).

"b) increasing the content of the dissolved CO_2 (pCO_2) in the medium during the production phase of the eukaryotic cells to a second value to increase the amount of bG0 structures and to decrease the amount of bG1 structures, relative to the amounts obtained by a method with no pCO_2 regulation,
wherein the first pCO_2 value is set at ≤10% and the second pCO_2 value is set at >10%
~~or decreasing the content of the dissolved CO_2 (pCO_2) in the medium during the production phase of the eukaryotic cells to a second value to decrease the amount of bG0 structures and to increase the amount of bG1 structures, relative to the amounts obtained by a method with no pCO_2 regulation~~."

Claim 1 of **auxiliary request 3** reads as claim 1 of auxiliary request 2 except for step b), which reads as follows (differences highlighted by the board, using underlining for additions and strike-through for deletions).

"b) increasing the content of the dissolved CO_2 (pCO_2) in the medium during the production phase of the eukaryotic cells to a second value to increase the amount of bG0 structures and to decrease the amount of bG1 structures, relative to the amounts obtained by a method with no pCO_2 regulation,
wherein the first pCO_2 value is set in the range of 3.5% to 6.5% ~~at ≤10%~~, and the second pCO_2 value is set 12% to 35%~~at >10%~~."

VII. The following documents are referred to in the present decision.

D1: WO 95/12684
D2: Zanghi *et al.*, Biotechnol. Bioeng., 65(2), 1999, pages 182-191.

VIII. The appellants' arguments, where relevant to this decision, may be summarised as follows.

Main request - Claim 1
Claim interpretation

The core of the invention was the influencing of galactosylation, as also acknowledged by the respondent. Thus, the term "controlling" was to be interpreted as "influencing".

In claim 1, the purpose of the method merely stated the effect that inevitably arose when carrying out method steps a) and b). According to the patent, that purpose was achieved simply by regulating nothing more than pCO_2 (see paragraph [0021]), without any additional steps being implied (see paragraph [0022]). There was no indication in claim 1 or in the description that the

claimed method contained additional steps. In particular, there was no indication of how "controlling" was to be carried out.

In decision T 1930/14, the board considered such a situation and decided that the purpose of the method was not a limiting feature of the claim. Moreover, the board in decision T 304/08 considered that the purpose of the method as stated in the claim did not imply any technical features. In decision T 1931/14, the board concluded that the purpose stated in a method claim could define an application of a method or, alternatively, the effect inevitably arising from carrying out the method steps. The latter applied to claim 1.

Novelty (Articles 100(a) and 54 EPC)

Documents D1 and D2 disclosed the method steps a) and b) of claim 1, including distinct growth and production phases.

The structures bG0 and bG1 were part of the preamble of claim 1 and therefore not a feature of the claimed method. Thus, in considering the question of novelty it was irrelevant whether the cited prior-art documents disclosed bG0 and bG1 structures. These structures were the result of carrying out the method steps a) and b). Therefore, for the claim to lack novelty it sufficed that these same steps were disclosed in a prior-art document.

Furthermore, the patent and document D1 both used CHO cells, and so the respective methods resulted in identical glycosylation patterns.

Therefore, the subject-matter of claim 1 was not novel in view of each of documents D1 and D2 (see document D1, page 5, lines 4 to 8 and the whole of example 1, in particular on page 10, line 35 (CHO cells), page 13, lines 12 to 15 (CO_2 during growth phase), page 14, lines 18 and 19 (CO_2 during production phase)).

Contrary to the respondent's argument, the wording of claim 1 did not require the culture medium to be the same in steps a) and b). Furthermore, feeding solutions were used in the patent (see example 3). This amounted to a change in the medium.

Auxiliary request 1 - Claim 1
Novelty (Article 54 EPC)

The respondent had not argued that the additional feature was a further limitation of the method steps.

This feature defined the result of the increase in pCO_2 and was not limiting, for the same reasons as submitted for the purpose stated in claim 1 of the main request. Consequently, claim 1 was not novel in view of the disclosure in each of documents D1 and D2.

Auxiliary request 2 - Claim 1
Admittance into the appeal proceedings

There was no substantiation in the written proceedings as to why this request overcame the objections under Article 54 EPC. Moreover, in the context of Article 83 EPC, the passage in the reply to the appeals that was referred to by the respondent did not provide a substantiation of this request either.

Auxiliary request 3
Admittance into the appeal proceedings (Article 13(2) RPBA)

Admittance of this request was governed by Article 13(2) RPBA, which required exceptional circumstances. No exceptional circumstances had been put forward. Nor were there any, since the objections under Article 54 EPC were present from the outset of the appeal.

For the purpose of procedural economy, and given the complexity of new issues raised, the request should not be admitted into the proceedings. The new features represented a selection from the ranges specified in dependent claim 5 of the patent as granted. The combination of these selected ranges with an increase in pCO_2 had not previously been present in the claims. Claim 1 did not comply with the requirements of Articles 123(2) and 84 EPC.

IX. The respondent's arguments, where relevant to this decision, may be summarised as follows.

Main request - Claim 1
Claim interpretation

The core of the invention was that galactosylation could be influenced by pCO_2. The purpose stated in the claim required the bG0 and bG1 profile to be determined and controlled. These steps of determining and controlling were implicit in the claim. Therefore, the purpose of "controlling the quality and quantity" was a feature of the method defined in claim 1.

Paragraph [0021] of the patent did not support the appellants' interpretation of the claim, since it referred to "regulating" the parameter pCO_2, and thus used a term similar to "controlling". Controlling of processes generally required adapting the process parameters in order to obtain the desired result, in the present case a desired glycosylation profile.

As in the case underlying decision T 1931/14, the purpose of the method implied method steps in addition to the steps recited in the claim. The claim was directed to a method of controlling and not to a method of production.

Novelty (Articles 100(a) and 54 EPC)

Claim 1 was novel over the disclosure in each of documents D1 and D2, for the following reasons.

These documents did not disclose proteins displaying bG0 and bG1 structures.

Additionally, neither of these documents disclosed that method steps a) and b) were both carried out in the same medium. On the contrary, in both documents the method involved a complete exchange of the medium between steps a) and b). This was to be distinguished from changes to the medium caused by addition of feed, as in example 3 of the patent. Since claim 1 referred in step b) to "the medium", it required the medium to be the same in steps a) and b). Therefore, the claim was novel.

As regards document D2, there was no disclosure of a recombinant protein or of a distinction between a

growth and a production phase. These were additional differences from the method in claim 1.

Auxiliary request 1 - Claim 1
Novelty (Article 54 EPC)

The additional feature further defined the steps of controlling. These should be taken into account as steps of the method defined in claim 1. Since these steps of controlling were not disclosed in documents D1 and D2, claim 1 was novel.

Auxiliary request 2
Admittance into the appeal proceedings

This request was filed in response to the objection under Article 83 EPC in the statement setting out the grounds of appeal of appellant II (see pages 19 to 20).

The reasons for filing the request were provided with the reply to the appeals (see page 3, point 2, last sentence).

Auxiliary request 3
Admittance into the appeal proceedings (Article 13(2) RPBA)

The features added to claim 1 of this request were present in claim 5 of the patent as granted. The claimed method included two distinct set values for pCO_2. The higher-ranking requests also included different set values for the growth and production phases, so this feature did not give rise to new aspects not yet discussed.

X. Appellant I and appellant II requested that the decision of the opposition division be set aside and the patent be revoked in its entirety.

The respondent requested that the decision of the opposition division be upheld and the patent be maintained as granted (main request), or, alternatively, that the patent be maintained in amended form on the basis of the claim sets according to auxiliary requests 1 to 3, wherein auxiliary request 1 was filed with the reply to the appeals, auxiliary request 2 was filed as auxiliary request 5 with the reply to the appeals, and auxiliary request 3 was filed during the oral proceedings.

Reasons for the Decision

Introduction

1. The patent relates to the preparation of proteins by mammalian cell culture. It aims at providing proteins with desired glycosylation profiles, specifically in relation to bG0 and bG1 structures. These structures are oligosaccharides characterised by specific arrangements of the constituting sugars and the presence or absence of galactose (see paragraph [0055] and table 3). According to the patent, a method is provided "*that allows to control the glycosylation profile in products produced in bioreactors* [...] *by only one parameter that is optionally easily set and regulated*" (see paragraph [0019]). The parameter in question is the content of dissolved carbon dioxide (pCO_2, which in the context of the invention is

synonymous with carbon dioxide partial pressure) (see paragraphs [0021] and [0042]).

Main request – Claim 1
Claim interpretation

2. Claim 1 is directed to a method comprising steps a) and b). Method step a) specifies conditions for cell growth, namely pCO_2 set to a first value (cell-growth phase), and method step b) specifies conditions for the production of a glycosylated polypeptide, namely pCO_2 set to a second value, which must be different from the first value (production phase). The purpose of the method as stated in claim 1 is "*controlling quality and quantity*" of posttranslational modifications of the protein that is produced, selected from bG0 structures and bG1 structures.

3. The parties disagreed on whether the stated purpose was a technical feature limiting the claimed method.

4. Claim 1 is directed to a method in which all the method steps relate to the preparation of a product. The question arises as to whether the claim defines a method of production, regardless of the purpose stated in the claim. The purpose as stated in claim 1 is "*controlling the quality and quantity*". The respondent argued that the term "controlling" implied method steps in addition to the explicit steps a) and b). Specifically, it implied steps of determining and controlling the bG0/bG1 structures. In its written submission, the respondent argued that controlling required determination and comparison of the bG0 and bG1 profile with a desired profile, possibly involving adjusting the process parameters.

5. The board does not share this view, for the reasons given below.

5.1 Despite the fact that "controlling" might mean measuring product characteristics, or measuring followed by adjusting the value of a process parameter if there is a deviation from the desired product characteristics, an alternative meaning is "achieving" or "obtaining" a product with the desired characteristics by means of pre-defined suitable parameter values and process steps. Therefore, the question to be addressed is which of the meanings applies in the case at hand.

5.2 There is no indication in claim 1 or elsewhere in the patent that "controlling" is to be given the meaning proposed by the respondent. No passages in the patent were put forward in support of this meaning.

5.3 According to the description of the patent, the method is characterised by a pCO_2 "maintained at a first value" or "first set-point" during the growth phase, which is increased or decreased to a "second set-point" in the production phase (see paragraph [0022]).

Claim 1 defines a method in which pCO_2 "is at a first value during the initial growth phase", in step a), and is at a "second value" in step b).

Thus, the method as disclosed in the description and as claimed involves a cell-growth phase and a production phase, both at pre-set pCO_2 values. There is therefore no indication of adjusting the values during cultivation, as feedback in response to deviating product characteristics. In this context the parties

disagreed on the meaning of the passage on paragraph [0021] that reads "[...] *the following method according to the invention: A method to control quality and quantity of posttranslational modifications selected from bG0 and bG1 struutres* [sic]*, as manifested in CEX profiles simply by regulating nothing more than* pCO_2". The board concurs with the appellants that this passage presents the method as relying solely on the parameter pCO_2 to achieve a desired glycosylation profile. Therefore this passage cannot support the respondent's claim interpretation, but rather is supportive of the appellants' interpretation.

5.4 In light of the above, the board concludes that claim 1, which recites only steps of production, does indeed define a method of production, and that the purpose of controlling quality and quantity of posttranslational modifications is not a limiting feature of the method.

6. The respondent argued that the conclusions in decision T 1931/14, in which the board held that the purpose stated in the claim was a limiting feature of the method, were applicable to the present case.

7. In decision T 1931/14, the board concluded that "[...] *in the context of a method it is important to differentiate between different types of stated purpose, namely those that define the application or use of a method, and those that define an effect arising from the steps of the method and implicit therein.*" (Reasons 2.2.4). The board held that in the first type the stated purpose represented a technical limitation of the method, whereas in the second it had no limiting effect.

8. In line with decision T 1931/14, the question addressed by the board in the case at hand was whether the purpose stated in claim 1 arose when carrying out the method steps explicitly defined in the claim. For the reasons set out above (see point 5.), the board came to the conclusion that this was the case. The present case resembles the one considered in decision T 304/08, where the board considered a claim to a method with the stated purpose of "reducing malodor associated with a disposable absorbent product". The board held that the claim was not a "use claim" in the sense of decision G 2/88 of the Enlarged Board, which related exclusively to claims directed to the use of a substance for achieving an effect. Instead, the claim before the board included a step resulting in the production of a product and was thus a process claim within the meaning of Article 64(2) EPC (Reasons 3.3.3.). This assessment was the determining point leading the board to conclude that the stated purpose did not have a limiting effect on the claim (Reasons 3.3.3 and 3.3.5).

Novelty (Articles 100(a) and 54 EPC)

9. For the assessment of novelty, the appellants relied on documents D1 and D2.

10. Document D1 concerns the production of glycoproteins by cell culture, and aims at providing methods which enable control of the product sialylation in particular. Specifically, the level of sialic acid in the product is manipulated by monitoring and adjusting the level of CO_2 during the cell culture (see page 1, first paragraph and page 5, lines 4 to 8). The method is exemplified with the production of erythropoietin in CHO cell culture. Experiments were carried out to

investigate the effect of six different pCO_2 levels on the product sialic acid composition (see example 1 on page 10, last paragraph and page 16, second paragraph). The method involved a cell-growth phase for 4 to 6 days at 5% or 10% pCO_2 (see page 13, lines 12 and 13). After the growth phase, a production phase was carried out at one of the six pre-set pCO_2 levels. For example, for the "runs 1.1 to 1.6" the pCO_2 was respectively 5, 10, 69, 75, 153 and 160 mmHg (see page 13, last sentence "*After the growth period* [...] *the treatment media as described in Table 1 was added*", Table 1, figure 6 and page 14, first paragraph, referring to carbon dioxide "*adjusted* [...] *according to the desired pCO_2 level*"). The pCO_2 values, which were measured daily, are depicted in figure 6. It can be seen that the values are set at the start and then fluctuate (see also description of figure 6 on page 7, penultimate paragraph and corresponding description on page 16, second paragraph). Thus, in spite of the use of the wording "monitoring" and "adjusting" in the general description of the method, in example 1 the pCO_2 level is set at the start of the growth phase with no further adjustments involved. The authors conclude that product sialylation does indeed vary with pCO_2 (see figure 8 and corresponding discussion on page 18, last paragraph to page 19, second paragraph).

In summary, document D1 discloses a method for the production of a glycoprotein by CHO cell culture, involving a cell-growth phase at a first pre-set pCO_2, followed by a production phase at a second pre-set pCO_2. The production phase pCO_2 may be set at a level above or below the growth phase level, depending on the desired product characteristics, specifically sialylation. Hence, document D1 discloses all the

features in steps a) and b) of claim 1 before the board.

11. The respondent did not dispute that document D1 disclosed the method steps a) and b), insofar as it disclosed different pre-set pCO_2 values for the growth and production phases. Instead, it argued that this document did not disclose proteins displaying bG0 and bG1 structures or controlling bG0 and bG1 structures. However, in view of the board's interpretation of claim 1 as set out in point 5.4, the method disclosed in document D1, which also results in the production of a glycoprotein by eukaryotic cell culture, and involves the same method steps a) and b), is not distinguishable from the claimed method, regardless of statements in claim 1 as to the purpose of the method. Hence, claim 1 is not novel in view of the disclosure in document D1.

12. Additionally, the respondent argued that claim 1 was novel because it required that the same medium be used in steps a) and b), whereas document D1 clearly disclosed a change in medium between these two steps. However, the board does not agree that claim 1 requires this. In the board's view, "a suitable medium" in step a) and "the medium during the production phase" in step b) do not necessarily refer to the same medium without exchange of medium between the two steps.

13. The board concluded that the subject-matter of claim 1 is not novel in view of the disclosure in document D1. In light of this outcome, there is no need to address novelty in view of the disclosure in document D2.

Auxiliary request 1 - Claim 1
Claim interpretation

14. In claim 1 of this request, step b) includes the two alternatives of increasing or decreasing the pCO_2 to a second value during the production phase, as present in claim 1 of the main request. Additionally, it includes the wording "*to increase the amount of bG0 structures and to decrease the amount of bG1 structures, relative to the amounts obtained by a method with no pCO_2 regulation*" in relation to an increase of pCO_2 in the medium, and "*to decrease the amount of bG0 structures and to increase the amount of bG1 structures, relative to the amounts obtained by a method with no pCO_2 regulation*" in relation to a decrease of pCO_2 in the medium.

15. In the board's view, the additional wording further defines the purpose of the claimed method.

16. In agreement with this, the respondent's arguments in relation to this claim request address the purpose of controlling.

17. However, in the present case the further definition of the purpose of the method, i.e. the purpose of increasing or decreasing pCO_2, does not introduce any additional method steps. In the board's view, the desired glycosylation profile as set out in claim 1 is still directly obtained by carrying out the method steps a) and b).

Novelty (Article 54 EPC)

18. In light of the claim interpretation as set out in the preceding point, the conclusion drawn in respect of

claim 1 of the main request applies here too. In claim 1 of the main request, step b) already involved an increase or decrease of pCO_2. The conclusion that the subject-matter is not novel in view of the disclosure in document D1 applies equally here.

Auxiliary request 2
Admittance into the appeal proceedings

19. This request was filed with the reply to the appeals, as auxiliary request 5.

20. Compared to claim 1 of the main request, in claim 1 of this request one of the alternatives in step b) has been deleted. As such, step b) relates only to increasing pCO_2 during the production phase. Further, the values for pCO_2 are set at ≤10% for the first value and >10% for the second value.

21. According to the respondent, the request was filed to address an objection under Article 83 EPC. To indicate how it addressed the objection, the respondent referred to a passage in its reply to the appeals, page 3, point 2.

22. The passage in question cannot provide reasons why the request overcomes objections under Article 54 EPC, since it relates solely to objections under Article 83 EPC. Moreover, it does not establish a causal link between the features in claim 1 of the request and any reasons why an objection under Article 83 EPC is overcome. Therefore, no substantiation was given that related to the additional features or to the objection under Article 54 EPC.

23. Since this request was newly filed with the reply to the appeals, the provisions of Article 12(4) RPBA are relevant to its admittance. Moreover, Article 12(3) RPBA requires the parties to present their complete case with the grounds of appeal and the reply to it. In the present case, any substantiation of how the request overcame any objections was lacking. Therefore, the board decided not to admit the request into the appeal proceedings.

Auxiliary request 3
Admittance into the appeal proceedings

24. This request was filed at the oral proceedings before the board. Claim 1 differs from claim 1 of auxiliary request 2 in that the first and second pCO_2 values are set in the range of 3.5% to 6.5% and 12% to 35% respectively.

25. The respondent has not presented any cogent reasons that could convince the board of the presence of exceptional circumstances for filing this request at this stage of the appeal proceedings, as required by Article 13(2) RPBA.

26. Moreover, the selection of ranges inserted into claim 1 gives rise to new issues to be considered.

27. The board accordingly decided to not take this request into account.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated