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**Datasheet for the decision
of 6 October 2022**

Case Number: T 2524/19 - 3.3.08

Application Number: 12738674.6

Publication Number: 2726600

IPC: C12P21/02, C12N5/00, C12P21/00,
C07K16/00

Language of the proceedings: EN

Title of invention:
MAMMALIAN CELL CULTURE

Patent Proprietor:
Amgen Inc.

Opponent:
Strawman Limited

Headword:
Mammalian Cell Culture/AMGEN

Relevant legal provisions:
EPC Art. 56, 84, 111(1), 123(2)
RPBA Art. 12(4), 11

Keyword:

Main request and auxiliary requests 1, 1a, 2, 2a, 3, 3a and 4
- Inventive step (no)
Auxiliary request 3b - added subject-matter (yes)
Auxiliary requests 5 to 7 - clarity (no)
Remittal (no)

Decisions cited:

T 0967/97, T 0578/06, T 0021/08, T 0716/08, T 1742/12,
T 1174/15, T 0418/17, T 1174/18, T 1012/19, T 0405/14

Catchword:



Beschwerdekammern

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Case Number: T 2524/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 6 October 2022

Appellant:

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Decision under appeal:

**Decision of the Opposition Division of the
European Patent Office posted on 9 July 2019
rejecting the opposition filed against European
patent No. 2726600 pursuant to Article 101(2)
EPC**

Composition of the Board:

Chairwoman T. Sommerfeld
Members: D. Pilat
 A. Bacchin

Summary of Facts and Submissions

- I. European patent No. 2 726 600 is based on European patent application No. 12 738 674.6, originally filed as international patent application published as WO 2013/006479. The patent was opposed on the grounds of Article 100(a) in conjunction with Articles 54 and 56 EPC, and of Article 100(b) EPC.
- II. The present appeal has been lodged by the opponent (appellant) against the decision of the opposition division rejecting the opposition.
- III. With its reply to the statement of grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed (main request) and maintained auxiliary requests 1 to 11 filed on 30 April 2018 and auxiliary request 7a filed on 15 March 2019. Furthermore, it submitted new auxiliary requests 1a, 2a, 3a, 3b.
- IV. Oral proceedings before the board were held in mixed-mode, with the agreement of the parties, the respondent and the board being present at the premises of the Boards of Appeal and the appellant participating remotely. At the end of the oral proceedings, the respondent withdrew auxiliary request 7a and 8 to 11.
- V. The **main request** consists of the patent as granted. Claim 1 of the main request reads as follows:

"1. A method of culturing mammalian cells expressing a recombinant protein comprising;

establishing a mammalian cell culture in a serum-free culture medium in a bioreactor by inoculating the bioreactor with at least 0.5×10^6 to 3.0×10^6 cells/ml in a serum-free culture medium;
growing the mammalian cells during a growth phase and supplementing the culture medium with bolus feeds of a serum-free feed medium
starting perfusion on or about day 5 to on or about day 9 of the cell culture, and
maintaining the mammalian cells during a production phase by perfusion with a serum-free perfusion medium, wherein the packed cell volume during the production phase is less than or equal to 35%."

Claim 1 of **auxiliary request 1** differs from claim 1 of the main request in that the term "or about" from "on or about day 9" was deleted.

Claim 1 of **auxiliary request 1a** differs from claim 1 of the main request essentially in that "wherein" was replaced by "and maintaining".

Claim 1 of **auxiliary request 2** differs from claim 1 of the main request in that the packed cell volume during the production phase is further characterised as being not lower than 10%.

Claim 1 of **auxiliary request 2a** combines the amendments of auxiliary requests 1a and 2.

Claim 1 of **auxiliary request 3** differs from claim 1 of the main request in that the packed cell volume during the production phase is further characterised as being not lower than 20%.

Claim 1 of **auxiliary request 3a** combines the amendments of auxiliary requests 1a and 3.

Claim 1 of **auxiliary request 3b** differs from claim 1 of auxiliary request 3a in that the following feature was added: "wherein the growth phase occurs at a temperature from about 35°C to about 38°C and the production phase occurs at a temperature from about 30°C to about 34°C".

Claim 1 of **auxiliary request 4** differs from claim 1 of the main request in that it further specifies that "... the viable cell density of the mammalian cell culture at a packed cell volume of less than or equal to 35% is 10×10^6 cells/mL to 80×10^6 cells/mL".

Claim 1 of **auxiliary requests 5 and 6** differs from claim 1 of the main request in that it is further specified that "... the viable cell density at the transition state between the growth and production phase and during production phase at a packed cell volume less than or equal to 35% is 20×10^6 cells/mL to 80×10^6 viable cells/mL" or "... is 30×10^6 cells/mL to 80×10^6 viable cells/mL", respectively.

Claim 1 of **auxiliary request 7** differs from claim 1 of auxiliary request 6, in that it further specifies that the packed cell volume during the production phase is not lower than 20%.

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

D2: Huang, E.P. *et al.* Biotechnology and Bioengineering, vol.88, n°4, pages 437 to 450, (2004);

- D5 WO 2011/062926;
- D7 WO 2006/026445;
- D10 WO 2008/063892;
- D11 Stettler, M. et al. Biotechnology and Bioengineering vol.95, n°6, pages 1228 to 1233, 20 December 2006;
- D12 Excerpt of "VWR" International, Issue 16, pages 12-13, December 2006;
- D14 Hu S, et al. Cytotechnology. vol. 63(3) pages 47-58, Epub Feb 5, 2011;
- D24 Ozturk, S. Cytotechnology. vol. 22 pages 3-16, 1996.

VII. The submissions made by the **appellant** as far as relevant to this decision were as follows:

Main request - Article 100(a) in conjunction with Article 56 EPC

The closest prior art was document D2. It related to the same or at least a similar purpose as the claimed invention and had the most features in common with the claimed subject-matter.

The method of document D2 differed from the claimed subject matter in that it used an inoculation concentration of cells of 0.25×10^6 cells/ml rather than of 0.5×10^6 to 3.0×10^6 cells/ml and did not explicitly maintain the volume of packed cells at or less than or equal 35% during the production phase. It was contested that the inoculation cell density led to increased recombinant protein titers. The patent application could not plausibly demonstrate that the increased recombinant protein titers was tied to the specific inoculation cell density range used in the combined fed-batch/perfusion cell culture process

according to claim 1. Hence, the technical problem derivable from the technical effect had to be formulated as the provision of a further (or an alternative) combined fed-batch/perfusion process of culturing mammalian cells expressing a recombinant protein.

The skilled person knew from documents D5, D7, D10, D14 and D24 that another cell inoculation density might be selected and that space limitation was of relevance in high density cell culture systems. The challenge associated with the harvest of super density fed-batch cell culture was known in the art (document D5, paragraph [0100]). Moreover, there was no experimental data in the patent which established that the 35% upper limit of the PCV was not arbitrary. Thus the selection of the specific inoculation cell density range and PCV percent range according to claim 1 amounted to a mere arbitrary selection based on which no inventive step could be derived.

Auxiliary request 1a - Article 56 EPC

The closest prior art was document D2.

The method of document D2 differed from the claimed subject matter in that it used a inoculation concentration of cells of 0.25×10^6 cells/ml rather than of 0.5×10^6 to 3.0×10^6 cells/ml and did not disclose an active step of maintaining the packed cell volume during the production phase at less than or equal to 35%.

It was contested that the inoculation cell density led to increased recombinant protein titers and no technical effect could be attributed to this step which

was not already inherently contained in the "wherein" clause and could justify an inventive step. The patent application could not plausibly demonstrate that the increased recombinant protein titers was tied to the specific inoculation cell density range used in the combined fed-batch/perfusion cell culture process according to claim 1. Hence, the technical problem had to be formulated as the provision of a further (or an alternative) combined fed-batch/perfusion process of culturing mammalian cells expressing a recombinant protein.

The skilled person knew from documents D5, D7, D10, D14 and D24 that another cell inoculation density might be selected and that space limitation was of relevance in high density cell culture systems. The challenge associated with the harvest of super density fed-batch cell culture was known in the art (document D5, paragraph [0100]). Moreover, there was no experimental data in the patent which established that the maintaining of the PCV at less than or equal to 35% upper limit was not arbitrary. Thus the selection of the specific inoculation cell density range and PCV percent range according to claim 1 amounted to a mere arbitrary selection based on which no inventive step could be derived.

Auxiliary requests 2 and 3 - Article 56 EPC

Claim 1 was obvious when starting from document D2 in combination with document D5, which disclosed the use of a packed cell volume of equal or less than 35%, but not below 10% (paragraphs [0005], [0027] and [0038] as well as [0092] in combination with Figure 4).

Document D5 specified that a cell bed volume of 20% had typically a cell density of over 100×10^6 cells/mL (paragraph [0100]). Similarly, a PCV with a lower limit of at least 10% was inherently disclosed in document D2 (Figure 9; paragraph [0033] and claim 8 of the patent). Furthermore, there was no evidence in the patent that a lower limit of 10% of the claimed PCV range was associated with a technical effect.

Auxiliary requests 2a and 3a - Article 56 EPC

The newly selected PCV range was arbitrary as it could not be shown to be associated with a technical effect, therefore the subject-matter of claim 1 was obvious.

Auxiliary request 3b - Article 123(2) EPC

Claim 1 resulted from a selection of features among different possibilities whose combination had no basis in the originally filed application. Although the selected and claimed temperature had a basis on page 14, lines 4 to 7 of the patent application, this feature was never directly and unambiguously disclosed in combination with the lower limit of the packed cell volume during the production phase being less than or equal to 35%, "but not lower than 20%" selected from the list disclosed on page 8, line 34 to page 9, line 4 of the patent application.

Auxiliary request 4 - Article 56 EPC

Since the viable cell density during the production phase in the fed-batch/perfusion process of document D2 was already $> 10 \times 10^6$ viable cells/ml, the newly introduced definition was not a further distinguishing

feature and therefore could not confer an inventive step to the method claimed.

Auxiliary requests 5, 6 and 7 - Article 84 EPC

The terms "transition state", "growth" and "production phase" referred to different growth phases of mammalian cells. The term "transition state", newly introduced into claim 1, was ambiguous. Since the different growth phases or state of mammalian cells depended, inter alia, substantially on the constitution of the cell culture medium, which was undefined in claim 1, the skilled person could not determine whether the mammalian cell culture was already or not yet in a transition state. Hence, the scope of protection of claim 1 was unclear.

Remittal

The board should not remit the case for further prosecution of the auxiliary requests, as there were no special reasons for doing so and for reasons of procedural economy. Moreover, auxiliary requests 1a, 2a, 3a and 3b were late filed and with regard to substantiation of inventive step, the respondent merely referred to the arguments presented for the main request.

- VIII. The submissions made by the **respondent** as far as relevant to this decision were essentially as follows:

Main request - Article 100(a) in conjunction with Article 56 EPC

Document D5, directed to the same purpose as the patent of providing an "easy and inexpensive method of

controlling cell growth while increasing protein production" (paragraph [0004] of the patent), constituted the closest prior art. Should document D2 nevertheless be regarded as closest prior art it would still not be capable of depriving the claimed subject matter of an inventive step.

Document D2 described a system to increase product yield by enhancing gene expression of the gene encoding the recombinant protein. It focused on the metallothionein (MT) expression system and on the further development of the system for "high level production" without the use of cadmium. The extrapolated yield of recombinant hGH for the fed-batch/perfusion process of 840 mg/L was lower than the 1200 ± 100 mg/L achieved in a fed-batch only process in a bioreactor whilst the second perfusion run was fraught with experimental errors (page 449, left column third line, Figure 9; page 447 and 448). Thus, document D2 used a different approach to improve protein yield.

The difference between the method of claim 1 and of document D2 were (i) the inoculation cell density, and (ii) the packed cell volume (PCV) during the production phase being less than or equal to 35%. The distinguishing technical features were linked and had to be considered in combination in the context of the problem-and-solution approach.

Although the method of document D2 and of claim 1 were not exactly comparable, Examples 1 to 4 demonstrated that a method according to the claims yielded antibody titers of up to about 28 g/L, which exceeded by far the product titers of the prior art. This technical effect could be used for formulating the objective technical problem since it was plausibly derived from the patent

on the basis of experimental data or theoretical considerations - absolute proof was not necessary (Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, I.D.4.6, in particular decision T 578/06, Reasons 13, and T 716/08, Reasons 14 to 16). There was no evidence which showed that the inoculation cell density and PCV in the claimed method was incapable of positively influencing the protein titer yield to achieve higher product yields than in the prior art. The technical difference between the method of claim 1 and the method disclosed in document D2 had therefore to contribute to the technical effect.

The technical problem underlying the claimed invention could thus be formulated as the provision of a method of culturing cell for producing a protein at a very high yield up to 28 g/L (Figure 1C of the patent). The problem was plausibly solved, as evidenced by Examples 1 to 4 of the patent.

Obviousness

Starting from document D2 and faced with the technical problem identified above, the skilled person would not have found a pointer in documents D5, D7, D10 or D14 to solve this technical problem in an obvious manner and thereby arrive at the method of claim 1.

Document D2 did neither teach nor suggest a method of culturing mammalian cells with a packed cell volume during the production phase that was less than or equal to 35% or an inoculation cell density of 0.5×10^6 to 3×10^6 cells/L, let alone a combination thereof. The extrapolated protein yield of 840 mg/L obtained using the fed-batch/perfusion process in document D2 was substantially lower than what was achieved by the

method of claim 1 (Examples of the patent). Since the PCV was a function of cell density and the cell density was dependent on the initial inoculation cell density, the inoculation cell density and the PCV were technically linked. While high cell densities were associated with certain problems during harvest and downstream processing, these problems could be mitigated by maintaining the packed cell volume at less than or equal to 35% (paragraph [0040] of the patent).

Due to the relatively low cell density observed in document D2, the skilled person would not have considered it necessary to maintain the packed cell volume at less than or equal to 35%. Moreover, the skilled person would not trust the data of document D2, since it was technically flawed (page 448, left column, last 3 lines to right column) and would rather be taught by document D2 to use other strategies to increase protein yield, such as addition of butyrate (page 447, left column, second paragraph).

Even if the objective technical problem were only formulated as the provision of an alternative method for expressing a recombinant protein, still the improvement of the method per se, independently of any improvement over the prior art, would have been inventive. Again there was no pointer in documents D5, D7, D10, or D14 to arrive at a method of culturing mammalian cells of claim 1 combining i) an inoculation cell density that falls within the recited range of 0.5×10^6 cells/mL to 3.0×10^6 cells/mL, and ii) a packed cell volume during the production phase that is less than or equal to 35%.

Auxiliary request 1 - Article 56 EPC

Claim 1 was amended by deleting "or about" from "on or about day 9". This amendment limited the scope of protection claimed and the same arguments as for the main request applied.

Auxiliary request 1a - Article 56 EPC

Document D2 did not teach the active step of "maintaining" the PCV during the production phase. In the patent it was disclosed that this step avoided certain handling problems during the production process, such as maintaining the dissolved oxygen levels and foaming (paragraph [0040], lines 37 ff.). Document D24 did not teach why a limit of the PCV to less or equal to 35% was crucial.

Auxiliary requests 2 and 3 as well as 2a and 3a - Article 56 EPC

The arguments for inventive step presented for the main request applied mutatis mutandis to auxiliary requests 2, 2a, 3 and 3a. The selected PCV and the inoculation cell density resulted in an exceptionally high production titer (patent, paragraph [0040]). Absolute proof of the achievement of a technical effect and therefore of experimental data in support of an effect was not required for an effect to be plausible (T 578/06, reasons 13 to 18). Document D2 disclosed no lower limit of PCV and there was no pointer for it. It showed nowhere that the selected PCV range was critical for the recombinant protein production and that it would be capable of avoiding handling issues (as disclosed in paragraph [0040] of the patent). Document D24 on the other hand mentioned a cell concentration of 10×10^6 which corresponded to a PCV of about 1 to 10%. Example 2 of document D5 related to a fed-batch cell

culture process using extreme conditions to increase cell density. It did not relate to a combined fed-batch perfusion cell culture process.

Auxiliary request 3b - Article 123 (2) EPC

The amendment introduced in claim 1 found a basis on page 8, line 34 to page 9, line 4 and on page 14, lines 4 to 7 of the patent application.

Auxiliary request 4 - Article 56 EPC

The arguments presented for inventive step of the main request applied mutatis mutandis to the method of claim 1 of auxiliary request 4.

Auxiliary requests 5 to 7 - Article 84 EPC

The terms "transition state", "growth" and "production phase" were clear in that the skilled person had no difficulties in determining whether and when a mammalian cell culture was in a growth phase, production phase or in a transition state. The skilled person had no difficulties to determine when it was working within the bounds of claim 1.

Remittal

None of the auxiliary requests 1 to 7, filed with the patentee's response to the notice of opposition, was dealt with in opposition proceedings. Since the right to have a complete examination and to have issues be considered by two instances would not be complied with, there were special reasons justifying a remittal of the case to the opposition division (Article 11 RPBA 2020).

Reference was made to decisions T 1174/15 point 2 of the reasons and T 1174/18 point 9 of the reasons.

- IX. The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety. The appellant further requested that none of the auxiliary requests be admitted into the proceedings.
- X. The respondent requested that the appeal be dismissed. Alternatively, should the board set aside the appealed decision, then the respondent requested that the case be remitted to the opposition division for further examination. Alternatively it requested that the European patent be maintained on the basis of any of auxiliary requests 1, 1a, 2, 2a, 3, 3a, 3b, 4, 5, 6 and 7, auxiliary requests 1a, 2a, 3a and 3b having been filed with the response to the statement of grounds of appeal while the other auxiliary requests had been filed during opposition proceedings with letter dated 30 April 2018.

Reasons for the Decision

Main request - Article 100(a) in conjunction with Article 56 EPC

Closest prior art and technical problem

1. The purpose and objective of the invention is to provide "a method for culturing mammalian cells expressing a recombinant protein" which "provides greater control over cell growth to achieve high product titer cell cultures" (see patent, paragraphs [0001], [0004] and [0022], and claim 12 of the patent application).

2. According to the case law the closest prior art must be directed to the same purpose as the claimed invention, and, as a secondary consideration, should have the most relevant technical features in common (see Case law of the Boards of Appeal of the European Patent Office 10th edition 2022, in the following "Case Law", I.D. 3.1, first paragraph). Hence, document D2, which relates to the same or at least a similar purpose as the claimed invention, is an appropriate closest prior art document based on which a problem and solution approach can be elaborated. In this context, the board disagrees with the respondent that document D5 should be taken as closest prior art instead. Even if the respondent argued that document D2 was "too far" from the claimed invention or not close enough compared to another "closer" prior art document D5, the board notes that if the skilled person has a choice of several pieces of prior art which might lead to the invention, the rationale of the problem-solution approach requires that the invention be assessed relative to all these possible pieces of closest prior art, before an inventive step can be acknowledged (see e.g. T 967/97, Reasons 3.2; T 21/08, Reasons 1.2.3; T 1742/12, Reasons 6.6; T 1012/19, Reasons 22). A document selected by a party as a starting point for assessing inventive step cannot be excluded only because some seemingly more promising item of prior art is available (see T 405/14, Reasons 19). In fact, the choice of a less favourable prior art would render it more difficult, if at all possible, for the appellant to substantiate that the claimed invention is obvious. Should the invention be obvious to the skilled person from at least one of the prior art documents, in this case from document D2, then no inventive step can be acknowledged anyway.

- 2.1 The method described in document D2 differs from the claimed method in that it uses an inoculation concentration of cells of 0.25×10^6 cells/ml instead of a concentration ranging from 0.5×10^6 to 3.0×10^6 cells/ml and does not state that the volume of packed cells is to be maintained at less than or equal to 35% during the production phase. This was not contested.
- 2.2 The respondent argued that Examples 1 to 4 of the patent provided evidence that a method according to the claims yielded antibody titers of up to about 28 g/L, which exceeded by far the product titers of the prior art. The board agrees but notes that the data in the patent does not allow to attribute the high yield of recombinant protein obtained in the Examples to the distinguishing features over the prior art. The numerous experimental differences between the cell cultures reported in examples 1 to 4 prevent any conclusion as to which of the selected variable(s) caused the higher protein yield. The cell line and the recombinant human growth hormone (hGH) are only two of these additional differences. Without control experiments, the separate fed-batch and perfusion processes reported in Examples 1 to 4 do not allow any conclusion as to whether any effect stems from a combination of both cell culture processes or from any of the selected experimental variables alone or in combination.
- 2.3 In the absence of any evidence establishing that the protein yield titers of a method of culturing mammalian cells expressing a recombinant protein according to claim 1 is improved, because it used a particular inoculation cell density and was maintained at a specific packed cell volume during growth phase, in comparison to the prior art method, this alleged

improvement cannot be taken into account when assessing inventive step.

2.4 The respondent further argued that according to the case law (e.g. T 716/08 and T 578/06) there was no requirement for an absolute proof for a technical effect in a patent. The board notes that decision T 716/08 is concerned with whether the claimed solution actually solves the technical problem, i.e. whether the claimed subject-matter actually provides the desired effect, but not as to whether the technical differences between the claimed subject-matter and the closest prior art impart a technical effect. Decision T 578/06 highlights that the disclosure of experimental data or results in the application as filed and/or post-published evidence is not always required to establish that the claimed subject-matter solves the objective technical problem. The board considers that none of these decisions support the respondent's argument that a technical effect does not need to be attributed to the distinguishing features between the claimed subject-matter and the closest prior art. Moreover, the board also disagrees with the respondent's argument that it is on the appellant to prove that the technical difference fails to provide any improved protein titer yield. Rather, it is on the respondent, who wants to rely on this effect mentioned in the patent, to show that the claimed method leads to this advantageous effect when compared to the closest prior art.

2.5 Accordingly, the technical problem has to be formulated as the provision of a further (or an alternative) combined fed-batch perfusion process of culturing mammalian cells expressing a recombinant protein, as formulated by the appellant. The board can however also accept the respondent's formulation of the technical

problem underlying the claimed invention as being the provision of a method of culturing cells for producing a protein at a very high yield up to 28 g/L.

- 2.6 In view of Examples 1 to 4 of the patent, the board is convinced that the method of claim 1 solves the objective technical problem of providing a method of culturing cell for producing a protein at a very high yield up to 28 g/L.

Obviousness

- 2.7 It remains to be assessed whether or not the skilled person, in the expectation of solving the underlying technical problem, would have modified the teaching in document D2 by using an inoculation concentration of cells of 0.25×10^6 cells/ml instead of a concentration ranging from 0.5×10^6 to 3.0×10^6 cells/ml and by maintaining the volume of packed cells at less than or equal to 35% during the production phase, so as to arrive at the claimed method in an obvious manner.
- 2.8 Motivated to solve the technical problem, the skilled person would turn to documents disclosing methods of culturing mammalian cells, such as documents D5, D7, D10, D14, which disclose the use of different inoculation cell densities. Moreover, document D24 (page 4, second paragraph) mentions that mammalian cells occupy only 1 to 10% of the volume in cell culture having densities of 10^7 and 10^8 cells/ml, whereas the theoretical maximum cell density for mammalian cell culture was of about 10^9 cells/ml. This indicates that high density cell culture systems can be improved in relation to space limitation.

- 2.9 Since the objective technical problem identified above is the mere provision of a further method to the one disclosed in document D2, i.e. an alternative to the prior art, any feature or combination of features already conventional for that sort of method represents an equally suggested or obvious solution to the problem posed. The skilled person would recognise the solutions to this objective technical problem without inventive efforts, thus the "could/would-approach" does not apply. A pointer to the solution claimed is also not required. Hence, the claimed solution represents an obvious and consequently non-inventive method combining a selected inoculation cell density among all the equally likely and possible inoculation cell densities with a standard mammalian cell culture condition. The simple act of arbitrarily selecting one method among all the equally obvious alternative methods without inventive efforts lacks an inventive step (see Case Law, I.D 9.21.9).
- 2.10 The board notes that the packed cell volume mentioned in claim 1 is defined in paragraph [0033] of the patent with reference to document D11. This document establishes that a cell density of about 4×10^6 cells/ml had a PCV value of about 0.5% (see D11, Figure 3). Since the perfusion process in Figure 9a of document D2 describes a viable cell concentration reaching a maximum of 12.5×10^6 cells/ml, the packed cell volume in percent inherently never exceeded 35%, based on the correlation established in document D11.
- 2.11 The board accepts that higher cell densities produce greater amounts of recombinant protein but cause also harvest and downstream processing problems (see paragraph [0040] of the patent). However, even if document D2 only teaches low viable cell densities, of

maximally about 12×10^6 cells/mL (D2, Figure 9 (a)) compared to the ones achieved in the present patent, the skilled person is familiar with the challenge associated with the harvest of super density fed-batch cell culture and with the standard measures that could and would increase the protein yield (see document D5, paragraph [0100]).

2.12 The skilled person would have immediately recognised that a PCV of less than or equal to 35% during the production phase in a method of culturing mammalian cell culture to high density avoids potential harvesting problems and is just one of many possibilities for solving the problem identified above. This requires neither a pointer nor an incentive.

2.13 The board considers that absent any claimed restriction regarding the protein to be expressed and the minimum protein yield to achieve, the skilled person, faced with the technical problem of providing an alternative method to the method disclosed in document D2, could have selected at least one suitable inoculation cell density and standard culture conditions, which inherently had a packed cell volume less than or equal to 35% to arrive at a method of culturing cells for producing a protein at a very high yield up to 28 g/L. The method of document D2 expressing hGH inoculated with an arbitrary slightly higher inoculation cell density, as suggested in documents D5, D7, D10, D14, is just one of many equally obvious methods that is capable of solving the problem posed.

2.14 Even if, as argued by the respondent, errors were made during the second perfusion fermentation disclosed in document D2, all of them were subsequently corrected and adjusted (see page 448, right column to page 449,

left column, paragraph 1). Therefore, the board cannot see why some transient technical problems arising during the process, that were identified, corrected and otherwise adjusted, shall jeopardize the credibility of the process and the overall results achieved.

2.15 Finally, as regards the respondent's argument that document D2 rather suggests to use butyrate in order to enhance the recombinant protein output from the MT expression system, the board fails to see why this teaching should make the claimed method inventive. The skilled person faced with the problem of providing an alternative method to the one described in document D2, capable of producing a protein at a very high yield up to 28 g/L - encompassing protein yield of 840 mg/L as well - would have modified the method to arrive at one of the many possibilities which solves the problem identified above, regardless of whether the use of butyrate in a cell culture during fed-batch operation in a bioreactor would also be advantageous. The addition of further features which were not shown to be linked to a technical effect in a method cannot confer an inventive step.

2.16 From the above considerations the combination of document D2 with any of documents D5, D7, D10 or D14 renders the method of claim 1 obvious. The main request does not fulfil the requirements of Article 56 EPC.

Auxiliary requests - admittance

3. The appellant requested that none of the auxiliary requests be admitted into the appeal proceedings. All auxiliary requests were filed with the reply to the statement of grounds of appeal and therefore their admission is ruled by Article 12(4) RPBA 2007, which

gives the board the power to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the proceedings before the examining or opposition division.

- 3.1 In view of the board's conclusions (see below) on inventive step in relation to the auxiliary requests 1, 1a, 2, 2a, 3, 3a and 4, with regard to Article 123(2) EPC in relation to auxiliary request 3b and with regard to Article 84 EPC in relation to auxiliary request 5 to 7, the board sees no need to give details as to why it admitted these auxiliary requests into the appeal proceedings pursuant to Article 12(4) RPBA 2007.

Auxiliary request 1 - Article 56 EPC

4. No arguments were submitted by the respondent as to why the amendment consisting in the deletion of "or about" from "on or about day 9" conferred an inventive step. It follows that the reasoning provided for claim 1 of the main request is not affected by this amendment.

- 4.1 As a result, claim 1 of auxiliary request 1 does not involve an inventive step (Article 56 EPC).

Auxiliary request 1a - Article 56 EPC

5. The board fails to see how the newly introduced active step of maintaining the PCV during the production phase at less than or equal to 35% contributes to an inventive step.

- 5.1 Starting from the closest prior art document D2, a technical effect cannot be attributed to the introduction of said active method step in the method of claim 1. Thus, the underlying technical problem

still has to be formulated as the provision of a mere alternative method to the one disclosed in document D2. The skilled person confronted with the technical problem above would merely have had to choose to actively maintain the PCV value at a maximum of 35% during the production phase, which represents at best an obvious and consequently non-inventive choice among all the known and equally likely possibilities that solve the problem posed.

- 5.2 It follows that the rationale for the lack of inventive step for claim 1 of the main request is not affected by the amendment introduced in claim 1 of the auxiliary request 1a, with the consequence that also this request does not involve an inventive step.

Auxiliary requests 2 and 3 - Article 56 EPC

- 5.3 Claim 1 of these requests further defines the PCV as not being lower than 10% (auxiliary request 2) or 20% (auxiliary request 3). The board agrees with the respondent that no absolute proof is required for an effect to be considered plausible (T 578/06, Reasons 13 to 18), but notes that the patent provides no teaching whatsoever that renders at least plausible that such a PCV lower limit is associated with a technical effect. Thus, the underlying technical problem starting from document D2 has to be formulated as the provision of a mere alternative method to the one disclosed in document D2. The skilled person confronted with this technical problem and without any technical effect to achieve would only have had to choose to maintain the PCV from 35% to not less than 10% or 20% during the production phase; such PCV limits were inherently disclosed in D5 (paragraphs [0005], [0027] and [0038] as well as [0092] in combination with Figure 4), and in

document D2 (Figure 9), regardless of other prior art documents eventually disclosing lower PCV values. This represents only and simply an obvious and consequently non-inventive arbitrary choice among all the known and equally likely possibilities that solve the problem posed.

- 5.4 It follows that the rationale for the absence of inventive step for claim 1 of the main request is not affected by the amendment introduced in claim 1 of the auxiliary requests 2 and 3.

Auxiliary requests 2a and 3a - Article 56 EPC

6. Claim 1 of these requests combine the amendments of auxiliary requests 2 and 3, respectively, with the amendment of auxiliary request 1a. Since there is no technical effect associated with these additional features, taken individually or in combination, the board considers that the underlying technical problem still has to be formulated as the provision of a mere alternative method to the one disclosed in document D2. The skilled person confronted with this technical problem would only have had to choose to actively maintain the PCV from 35% to not less than 10% or 20% during the production phase, which represents only an obvious and consequently non-inventive arbitrary choice among all the known and equally likely possibilities that solve the problem posed.

- 6.1 As a result, claim 1 of auxiliary requests 2a and 3a does not involve an inventive step (Article 56 EPC).

Auxiliary request 3b - Article 123(2) EPC

7. In addition to the amendments of auxiliary request 3a, claim 1 of this request further requires that the growth phase occurs at a temperature from about 35°C to about 38°C and the production phase occurs at a temperature from about 30°C to about 34°C. According to the respondent, said amendment found basis on page 8, line 34 to page 9, line 4 and on page 14, lines 4 to 7 of the application as filed, which read, respectively:

"The desired packed cell volume maintained during the production phase is equal to or less than 35%. In a preferred embodiment the packed cell volume is equal to or less than 30%. In another preferred embodiment the packed cell volume is equal to or less than 20%. In another preferred embodiment the packed cell volume is equal to or less than 15%. In yet another preferred embodiment the packed cell volume is equal to or less than 10%."

"A growth phase may occur at a higher temperature than a production phase. For example, a growth phase may occur at a first temperature from about 35°C to about 38°C, and a production phase may occur at a second temperature from about 29°C to about 37°C, optionally from about 30°C to about 36°C or from about 30°C to about 34 °C."

- 7.1 The board considers that while the specific PCV sub-range and the specific temperature range may be considered disclosed in the above mentioned passages of the application as filed, their combination, i.e. the specific claimed combination of a selected PCV part-range and of a specific temperature range for the growth and production phase is not directly and unambiguously, neither explicitly nor implicitly, derivable from the patent application.

7.2 Thus, auxiliary request 3b contravenes Article 123(2) EPC.

Auxiliary request 4 - Article 56 EPC

8. Claim 1 of auxiliary request 4 further defines the cell density of the mammalian cell culture. Since the viable cell density during the production phase in the fed-batch/perfusion process of document D2 is already $> 10 \times 10^6$ viable cells/ml (see Figure 9(a) of document D2), the additional feature introduced in claim 1 specifying that the viable cell density at a packed cell volume of less than or equal to 35% is 10×10^6 to 80×10^6 cells/ml during the production phase, is not a further distinguishing feature in relation to document D2. Thus, auxiliary request 4 also lacks an inventive step.

Auxiliary requests 5 to 7 - Article 84 EPC

9. In these requests, claim 1 was amended so that it further specifies that "... the viable cell density at the transition state between the growth and production phase and during production phase at a packed cell volume less than or equal to 35% is 20×10^6 cells/mL to 80×10^6 cells/mL viable cells/ml" (auxiliary request 5) or "... is 30×10^6 cells/mL to 80×10^6 cells/mL viable cells/mL" (auxiliary requests 6 and 7). The appellant argued that this amendment, which originated from the description, rendered the claim unclear because the terms "transition state", "growth phase" and "production phase" were ambiguous and the skilled person would not know, without the definition of the cell culture medium, at which time of the cultivation process the mammalian cell would be in each of these states or phases.

9.1 A mammalian cell culture undergoes four main different cell growth phases comprising a latent phase, an exponential growth phase, a stationary phase and death phase. In the cell growth phase, the cells proliferate and increase rapidly in number, whereas they redirect their resources towards recombinant production during the cell production phase. The transition state must describe the passage from a cell growth phase to a cell recombinant production phase, i.e. a cell culture essentially replicating to a cell culture essentially producing a recombinant protein. Such a cell culture transition is not immediate but is a progressive process requiring a yet undefined period of time, where the cells in the cell culture are gradually adapting to the circumstances by modifying their cell metabolism. Since the term transition state is not objectively defined in the prior art or in the patent and cannot be assigned clear boundaries, the skilled person cannot objectively determine whether the cells in the cell

culture are still in a growth phase or already in a transition phase or yet in a phase of protein recombinant production. Hence, the skilled person cannot establish at which time of the growth phase of the cell culture process the viable cell density, with a packed cell volume less than or equal to 35%, must or must not range between 20×10^6 or 30×10^6 cells/mL to 80×10^6 viable cells/mL and thus whether he is working within or outside the scope of claim 1.

- 9.2 Hence, the requirements of Article 84 EPC in auxiliary requests 5 to 7 are not met.

Remittal

10. The respondent requested to remit the case to the opposition division should the board set aside the appealed decision. It was submitted that the auxiliary requests had not been discussed by the opposition division.
- 10.1 In accordance with Article 111(1) EPC the board may either exercise any power within the competence of the department which was responsible for the decision under appeal or remit the case to that department for further prosecution. Thus a request for remittal to the department of first instance is subject to the discretion of the board of appeal.

In addition, Article 11 RPBA 2020 provides that the board shall not remit a case to the department whose decision was appealed for further prosecution, unless special reasons present themselves for doing so.

- 10.2 In the present case the board considers that there are no special reasons for remitting the case to the

opposition division for further prosecution. It decides to exercise its discretion not to remit for the following reasons:

- 10.2.1 With regard to auxiliary requests 1, 1a, 2, 2a, 3, 3a and 4 the board finds that the amendments to the claims are not such that further substantive examination of that subject-matter is necessary. Indeed, although the decision under appeal was limited to the main request, the amendments introduced in this group of auxiliary requests do not alter the legal and factual framework concerning the inventive step discussion for the main request (see also T 418/17, Reasons 2.). The starting point for the assessment of inventive step is the same (document D2) and the formulation of the technical problem remains unchanged.
- 10.2.2 In particular, in view of the binding effect of the board's decision reversing the decision of the opposition division on inventive step of the main request, a remittal would not enable any additional considerations and examination of these requests by the opposition division on this issue.
- 10.2.3 With regard to the remaining auxiliary requests 3b, and 5 to 7 the board finds that although the primary object of the appeal proceedings is to review the decision under appeal in a judicial manner (see Article 12(2) RPBA 2020), there is no absolute right to have every issue decided at two instances. In the case in hand, the parties have submitted arguments in writing regarding the objections on Articles 123(2) and 84 EPC against these auxiliary requests and were therefore prepared to discuss them. Further, since the issues appear to be quite clear, a remittal to the opposition division, as requested by the respondent, does not seem

appropriate, in particular given the current state of the proceedings and the need for procedural economy.

10.2.4 The respondent cited two decisions in support of their request for remittal. In the first case, T 1174/18, it was acknowledged that the amendments which led to the amended claims were such that the interpretation of the claims was bound to change (see point 9. of the Reasons). Since the subject matter of the amended auxiliary request 7 had not been examined by the opposition division as to its patentability, a remittal to the first instance was justified and granted. On the contrary, in the case at hand, although the patentability according to Article 56 EPC of the main request had been assessed in opposition proceedings, the amendments introduced in any of the auxiliary requests 1 to 7 are such that the interpretation of the claims is not bound to change. Besides, the appellant had provided arguments in its statement of grounds of appeal as to why auxiliary requests 1 to 7 lacked an inventive step.

In the second case, T 1174/15, the board decided to grant the respondent's request for remittal of the case to the opposition division, because the appellant withdrew its request not to have it remitted to the first instance (see point 2. of the Reasons). Since the parties maintained contrary requests regarding the remittal of the case to the first instance, the cited decision is not applicable to the case at hand.

Thus, in view of the above considerations the board decided to exercise its discretion, pursuant to Article 111(1) EPC and Article 11 RPBA 2020, not to remit the case to the opposition division.

Conclusion

Since none of the requests on file is allowable the patent must be revoked.

Order

For these reasons it is decided that:

1. The appealed decision is set aside.
2. The patent is revoked.

The Registrar:

The Chairwoman:



L. Malécot-Grob

T. Sommerfeld

Decision electronically authenticated