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**Datasheet for the decision of 9 December 2025**

**Case Number:** T 1655/23 - 3.2.03

**Application Number:** 14708915.5

**Publication Number:** 2976418

**IPC:** C12M1/00, C12M1/12, C12M1/26, C12N7/00, C12N9/64

**Language of the proceedings:** EN

**Title of invention:**
A METHOD FOR PRODUCING A PRODUCT (E.G. POLYPEPTIDE) IN A CONTINUOUS CELL CULTURE FERMENTATION PROCESS

**Patent Proprietor:**
CMC Biologics A/S

**Opponent:**
Wilk, Thomas

**Headword:**

**Relevant legal provisions:**
EPC Art. 123(2), 83, 54, 56

**Keyword:**
Amendments - extension beyond the content of the application as filed (no)
Sufficiency of disclosure - (yes) - enabling disclosure (yes)
Novelty - (yes)
Inventive step - non-obvious alternative

**Decisions cited:**
T 0575/05, T 0817/11

**Catchword:**

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

**Boards of Appeal**

**Chambres de recours**

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**Case Number: T 1655/23 - 3.2.03**

# D E C I S I O N
# of Technical Board of Appeal 3.2.03
# of 9 December 2025

| | |
|---|---|
| **Appellant:** (Opponent) | Wilk, Thomas<br>c/o Zwicker Schnappauf & Partner<br>Patentanwälte PartG mbB<br>Hansastr. 32<br>80686 München (DE) |
| **Representative:** | Wilk, Thomas<br>ZSP Patentanwälte PartG mbB<br>Hansastraße 32<br>80686 München (DE) |
| **Respondent:** (Patent Proprietor) | CMC Biologics A/S<br>Vandtaarnsvej 83<br>2860 Søborg (Copenhagen) (DK) |
| **Representative:** | ZBM Patents - Zea, Barlocci & Markvardsen<br>Rambla de Catalunya, 123<br>08008 Barcelona (ES) |
| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 11 July 2023 rejecting the opposition filed against European patent No. 2976418 pursuant to Article 101(2) EPC.** |

**Composition of the Board:**

| | |
|---|---|
| **Chairman** | C. Herberhold |
| **Members:** | B. Miller |
| | J. Hoppe |

## Summary of Facts and Submissions

I. European patent No. 2 976 418 B1 (the patent) relates to a continuous chemostat fermentation process.

II. An opposition against the patent was filed on the grounds of Article 100(b)and (c) EPC and Article 100(a) EPC together with Articles 54 and 56 EPC.
The opposition division concluded that the grounds for opposition did not prejudice the maintenance of the patent and decided to reject the opposition.

III. The opponent (appellant) filed an appeal against the rejection of the opposition.

IV. Wording of the claims as granted according to the main request

Claim 1:

"A method for producing a product selected from a biopolymer expressed by a cell, an intracellular or extracellular product produced by a cell or microorganism, a periplasmatic product produced by a cell or microorganism, a cell or a microorganism in a bioreactor in a high-density chemostat fermentation process, wherein said bioreactor comprises:

i) a first outlet having a separation device allowing impurities with a size below the size of the product, and medium to be removed while retaining the product in the bioreactor;

(ii) a second outlet having a product harvest module allowing the product, cells, impurities and medium to be removed; and
(iii) an inlet for adding a medium;

wherein the method comprises the following steps:

(a) fermenting the cell expressing the biopolymer, the cell or microorganism producing the intracellular product, the cell, or microorganism producing the periplasmatic product, the cell, or the microorganism in the bioreactor in a suitable medium under suitable conditions, wherein during the fermentation impurities and medium are removed via the separation device, the product, cells, impurities and medium are removed via the product harvest module and new medium is added to replenish nutrients consumed by the cells or microorganisms and to equilibrate the medium removed during removal of impurities and harvesting the product; and
(b) the product is isolated from the harvested medium; and

wherein the cell density in the bioreactor during the fermentation reaches at least 5 million cells per ml medium."

Claim 14 reads:

"A method for producing a product selected from a biopolymer expressed by a cell, an intracellular or extracellular product produced by a cell or microorganism, a periplasmatic product produced by a cell or microorganism, in a first and a second

bioreactor in a high-density chemostat fermentation process, wherein said first bioreactor comprises:

i) optionally a first outlet having a separation device allowing impurities with a size below the size of the product, and medium to be removed while retaining the product in the bioreactor;
(ii) a second outlet having a product harvest module allowing the product, impurities and medium to be removed; and
(iii) an inlet for adding a medium;

wherein said second bioreactor comprises:

(iv) a third outlet having a separation device allowing impurities with a size below the size of the product, and medium to be removed while retaining the product in the bioreactor;
(v) a fourth outlet having a product harvest module allowing the product, impurities and medium to be removed; and
(vi) an inlet for adding a medium;
(vii) an inlet for adding cells and a medium from the first bioreactor;

wherein the first bioreactor is for growth of cells or microorganisms and the second bioreactor is for induction of production of the biopolymer, the intracellular or extracellular product, or the periplasmatic product, and wherein the first and second bioreactor operates in series,
wherein the method comprises the following steps:

(a) growing and optionally fermenting the cell expressing the biopolymer, the cell or microorganism producing the intracellular or

extracellular product, the cell or microorganism producing the periplasmatic product, the cell, or the microorganism in the first bioreactor in a suitable medium under suitable conditions, wherein during the growing and optionally fermentation impurities and medium are removed via the separation device, the product, impurities and medium are removed via the product harvest module and new medium is added to replenish nutrients consumed by the cells or microorganisms and to equilibrate the medium removed during removal of impurities and harvesting the product; and
(b) transporting the product, impurities and medium removed via the product harvest module to the second bioreactor, induction of production of the biopolymer, the intracellular or extracellular product, or the periplasmatic product, wherein during the production impurities and medium are removed via the separation device, the product, impurities and medium are removed via the product harvest module and new medium is added to replenish nutrients consumed by the cells or microorganisms and to equilibrate the medium removed during removal of impurities and harvesting the product
(c) the product is isolated from the harvested medium; and

wherein the cell density in the bioreactor during the fermentation reaches at least 5 million cells per ml medium."

V. Oral proceedings were held on 9 December 2025.

VI. At the end of the oral proceedings, the following requests were maintained by the parties.

The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed. In the alternative, it requested that the patent be maintained in amended form on the basis of one of auxiliary requests 1 to 5 as submitted with the letter of reply to the statement of grounds of appeal.

VII. The following documents cited during the opposition proceedings are of importance for the appeal proceedings:

D1: WO 2008/152075 A1

D2: EP 2 014 760 A1

D3: WO 2008/006494 A1

D4: WO 2005/095578 A1

D5: O. Henry et al., "Simpler Noninstrumented Batch and Semicontinuous Cultures Provide Mammalian Cell Kinetic Data Comparable to Continuous and Perfusion Cultures", Biotechnol. Prog. 24(4), 2008, 921-31

D6: WO 2009/023562 A2

D7: G.W. Hiller et al., "Cell Retention-Chemostat Studies of Hybridoma Cells-Analysis of Hybridoma Growth and Metabolism in Continuous Suspension Culture on Serum-Free Medium", Biotechnology and Bioengineering 42, 1993, 185-95

D12: P.E. Strandberg, "Examensarbete Mathematical models of bacteria population growth in bioreactors: formulation, phase space pictures, optimisation and control", ISSN 0348-2960, published on 13 May 2004

D14a: B. McNeil and L. M. Harvey, "Practical Fermentation Technology", John Wiley & Sons Ltd, 2008, Chapter 2

VIII. The appellant's arguments relevant for this decision can be summarised as follows.

(a) Amendments

The expression "high density" in claims 1 and 14 was used to specify the "chemostat fermentation process" rather than the "cell density". Furthermore, the application as originally filed specified that a high cell density "is a density of at least 15 mill cells/ml" that was only obtained when using specific flow rates. However, both the specific cell density and the specific flow rates had been omitted from claim 1, which represented an unallowable intermediate generalisation beyond the "high-density chemostat fermentation process" disclosed in the application as filed.

(b) Sufficiency

The patent did not contain a working example according to the invention. Example 2 did not disclose that any cells or impurities were removed via a second outlet for harvesting the product during fermentation. Moreover, it did not describe how the cell density could be reached during the chemostat processing mode. Therefore, Example 2 did not represent the method according to claim 1.

The lack of guidance could not be overcome by drawing on the common general knowledge.

D5 and D6 provided verifiable facts that raised serious doubts as to whether the skilled person was enabled to rework the process of claim 1.

The skilled person was faced with undue burden since the cell density would decrease during the high-density chemostat fermentation process. The patent did not contain any proof that a density of at least $5x10^6$ cells/ml, in particular $30x10^6$ cells/ml, had been reached in Example 2 of the patent. The patent lacked guidance on how to retain the cell number in the bioreactor vessel to make it credible that the claimed cell density of $5x10^6$ cells/ml could also be maintained.

The process of claim 14 could also not be reworked since without adding cells into the second bioreactor, cell fermentation could not take place.

(c) Novelty

The wording of claim 1 could be interpreted as referring to a process taking place in a bioreactor. The process could be performed under any conditions in a bioreactor suitable for use in a chemostat fermentation process.

The methods disclosed in D1 to D4 were suitable for chemostat fermentation.

In the perfusion fermentation process according to D1 and D2, an additional outlet ("bleed") was used. This process involved the continuous removal of cells via the bleed outlet from the bioreactor during the fermentation process, something which was typical for a chemostat process and was also required by claim 1 of

the patent. Furthermore, the continuous process according to D1 and D2 took place in a steady state. It thus qualified as a chemostat process, even if the term "chemostat process" itself was not explicitly used.

Therefore, claim 1 lacked novelty over the process of D1 and D2.

As to D3, the process C3 according to Example 3 reached a steady state. The cells were continuously removed by a bleed. Indeed, the variation of the cell density shown in Figure 3 of D3 was in the same range as the variation shown in Figure 5 of D5 for a chemostat process, this showing that the C3 process of D3 also kept the cell density constant - at least within the usual tolerances of a chemostat process. This argument based on the comparison of the figures in D3 and D5 should be admitted as it was a response to points raised in the Board's communication. To conclude, the fed-batch or perfusion process of D3 met all requirements of claim 1 of the patent and, hence, was a chemostat process in the sense of claim 1.

D4, similar to D1, related to a continuous perfusion process for culturing cells that reached a steady state. Biomass removal was carried out continuously or step-wise in which the rate of addition of the cell culture medium to the cell culture was the same as the biomass removal rate. Therefore, claim 1 also lacked novelty over D4.

(d) Inventive step

D3 represented the closest prior art.

Using a chemostat process provided no technical effect. For this reason alone, the subject-matter of claim 1 was not inventive.

Even if running a fermentation process under chemostat conditions were considered to have a technical effect, this would be the same as the technical effect obtained by the process of D3: increasing cell densities and thereby the productivity of the bioreactor (see paragraph [0010] of the patent and page 1, lines 26 to 27 of D3). Hence, the subject-matter of claim 1 was not inventive.

Alternatively, if the technical effect were to be taken into account when formulating an objective technical problem, this could be regarded as providing an alternative method for producing a product in a bioreactor.

D7 to D11 demonstrated that it was known in the art to continuously use a bleed outlet or a separation device, for example, to increase the cell density of viable cells and to remove impurities and waste from a bioreactor.
Therefore, modifying the process of D3 by using a bleed outlet or a separation device to increase cell density was obvious.

For the same reasons, it was also obvious to modify the perfusion process disclosed in documents D1, D2 and D4 into the claimed chemostat process.

Therefore, the subject-matter of claim 1 lacked an inventive step.

Building upon the argument starting from D3, the subject-matter of claims 6 and 14 also lacked an inventive step.

IX. The respondent's relevant arguments can be summarised as follows.

(a) Amendments

Claims 1 and 14 as granted were based on claims 1 and 14 as originally filed in which the expression "high-density" had been added. It was immediately apparent that the expression "high density" referred to the cell density in the bioreactor. This relative expression was a descriptive expression which was encompassed by the final feature of claims 1/claim 14, according to which the cell density in the bioreactor during fermentation reaches at least 5 million cells per ml ("mill cells/ml") medium. Only as a preferable embodiment did the application disclose a higher density of at least 15 million cells/ml.

The application did not specify that particular flow rates were necessary to reach high density. The expression "with the same or a different flow rate" on page 11, lines 8 to 15 did not provide any limitation but covered all possible combinations available to a skilled person, the in- and outflow being implicit in a continuous chemostat process. This disclosure on page 11 was further supported by the specification relating to the chemostat reactor on page 6, lines 22 to 30 and Figure 1 of the application.

(b) Sufficiency

The examples in the patent, particularly Example 2, provided the skilled person with sufficient information to rework the invention.

Moreover, a skilled person was aware that a chemostat fermentation process was controlled so that the growth rate of the microorganism was equal to the dilution rate, i.e. fresh medium was continuously added while liquid containing unused nutrients, metabolic products and cells were continuously removed at the same rate to keep the culture volume of the reactor and the harvest rate constant.

The appellant's objections regarding sufficiency of the process according to claim 1 were based on allegations and speculation.

With respect to claim 14, a skilled person would immediately recognise that the second bioreactor contained cells. This could be easily achieved either by using an additional inlet for cells as specified in claim 1 (see feature vii) and as disclosed in paragraph [0019] of the patent or by adding the product containing cells.

(c) Novelty

Claim 1 did not specify that the method took place in a bioreactor **for** a high-density chemostat fermentation process but rather required that the method be carried out in a bioreactor **in** a high-density chemostat fermentation process, i.e. under chemostat process conditions (the physiological environment was kept static during the fermentation process).

D1 to D4 disclosed continuous perfusion processes but not a chemostat process, i.e. a process running in a physiological steady state, as defined in claims 1 and 14 of the patent.

D1 did not disclose that the bleed was continuously removed under chemostat conditions ("in a chemostat fermentation process"), i.e. that the feed rate of the new medium equilibrated the amount of medium removed during the bleeding step. According to D1, bleeding took place during the initial starting phase of the fermentation process rather than during the harvesting phase. The examples of D1 did not disclose the method of claim 1 in which the product, cells, impurities and medium were removed via the product harvest module in a chemostat fermentation process.

Concerning D2, the same arguments applied as for D1.

D3 disclosed that cell culture conditions were chosen such that the growth rate and/or productivity of the cells were not limited and more preferable such that the concentration of at least one of the components of the cell culture medium remained essentially constant. However, D3 did not disclose that the overall process of D3, particularly process C3 of Example 3, was carried out under chemostat process conditions, where the physiological environment was kept static.

Moreover, D3 did not disclose that the bleed was continuously removed under chemostat conditions. As to the comparison between Figure 5 of D3 and Figure 5 of D5, this argument should not be admitted as it was not possible to address it without further elaboration of the underlying process conditions in D5, although it

was immediately apparent that in view of the different scaling in the two figures (logarithmic versus linear), no conclusions about an allegedly constant cell density of the C3 process in D3 could be drawn. Indeed, Figure 5 appeared to instead point to a once daily bleed.

Similar to D1, D4 disclosed a continuous perfusion process. It did not, however, reveal that culture medium was added under chemostat conditions to replenish the nutrients consumed by the cells or microorganism as specified in step a) of the process according to claim 1 of the patent.

(d) Inventive step

Starting from D3, the skilled person had no reason to fundamentally alter the process conditions of the perfusion fermentation process to achieve a chemostat fermentation process in which the chemical environment was kept static during the fermentation process, i.e. microorganisms/cells were grown in a physiological steady state. Since fundamentally changing the process conditions carried the risk of unforeseeable complications, a skilled person would not consider this an obvious modification when aiming to provide an alternative fermentation process. Analogous reasoning applied when starting from D1, D2 or D4 as the closest prior art.

## Reasons for the Decision

1. Main request - amendments (Article 100(c) EPC)

1.1 Claim 1 as granted is based on claim 1 as originally filed to which the expression "high-density" has been added. Claim 14 also refers to a method for producing a product in a "high-density" chemostat fermentation process. This relative expression can be considered descriptive and is encompassed by the final feature of claim 1/claim 14 according to which the cell density in the bioreactor during the fermentation reaches at least 5 million cells per ml ("mill cells/ml") medium.

The inclusion of the relative expression "high-density" does not alter the subject-matter compared to claim 1/ claim 14 as filed, which already defined the minimum cell density (at least 5 million cells per ml ("mill cells/ml") medium), albeit without explicitly specifying that the process was a "high-density" chemostat fermentation process.

1.2 The appellant argued that the expression "high density" was used to specify the "chemostat fermentation process" rather than the "cell density".

However, this argument is not convincing since a skilled person interprets the wording of a claim in its technical context and with a willingness to understand it. Considering the technical context of the patent, it is immediately apparent that the expression "high density" refers to the cell density in the bioreactor during the chemostat fermentation process.

1.3 The appellant further argued that the application as originally filed (reference is made to the application as published, WO 2014/146933 A1 (the application)) defined on page 24, lines 26 to 27 that a high cell density, in particular a high viable cell density, "is a density of at least 15 mill cells/ml".

This argument is not persuasive because the application discloses on page 24 that a density of at least 15 million cells/ml is merely preferable. Hence, the application does not specify that "high density" must be interpreted as referring to a density of at least 15 million cells/ml.

1.4 Moreover, the application provides a basis for the amendment. On page 11, lines 8 to 17, it discloses the benefits (higher productivity) derivable from the use of a bioreactor equipped with a separation device. It states that "[t]his chemostat process may also be called herein a high-density chemostat or just HD chemostat".

Contrary to the appellant's arguments, the disclosure on page 11, lines 8 to 17 of the application does not provide a new, independent definition of the expression "chemostat fermentation process" which should apply in the patent instead of the commonly accepted meaning confirmed previously in the application (see the paragraphs from page 2, line 18 to page 3, line 2 and from page 8, line 28 to page 9, line 19, which correspond to paragraphs [0006] and [0021] as granted). Rather, the disclosure on page 11 explains why the process is referred to as a high-density chemostat and how the standard chemostat fermentation process is modified ("by having one outlet on a bioreactor

equipped with a separation device") to achieve an increased cell density.

1.5 The appellant further argued that on page 11, lines 16 to 17 the application explicitly referred to specific aspects of the process described previously ("This chemostat"), particularly the flow rates through a separation device and a product outlet. Due to this definition of flow rates, the application clarified that the high-density chemostat process was a continuous process. However, since amended claim 1 did not define these flow rates, it constituted an unallowable intermediate generalisation. Furthermore, the disclosure on page 11 of the application could be regarded as a new definition of the term "chemostat process" which should be considered instead of its commonly accepted meaning.

This argument is not convincing.

1.5.1 Claim 1 defines a high-density chemostat process. While this is a modified chemostat process run at higher cell densities ("high density"), it is still a chemostat process. In line with the common understanding of the skilled person - confirmed by the various documents on file such as D5 (see right-hand column on page 924), D12 (see chapter 2.2 on page 5) and D14a (see chapter 12.3) and the general explanations in the patent as granted (see paragraphs [0006] and [0021]) - a chemostat process is a continuous process, with a continuous inflow of medium and an outflow of cells and products, operating in a physiological steady state at a growth rate equivalent to the dilution rate. This equilibration determines the concentration of the cells.

The patent provides no disclosure or definition that contradicts the common understanding of what a chemostat process is. Rather, the patent confirms that the chemostat process is run according to its commonly accepted meaning, except for the clearly identified modifications (an additional outlet with a separation device and high cell density); see Example 2 (chemostat process according to the invention) in comparison to Example 1 (chemostat process according to the state of the art) or, for example, paragraph [0110] of the patent.

Therefore, the reference to a chemostat process in claim 1 clearly defines that the claimed process is a continuous process. It follows that during the process of claim 1, medium flows continuously in and out through the inlet and outlets as defined in that claim.

Interpreting the technical terms in claim 1 of the patent in accordance with their commonly accepted meanings, which are not put into question by the accompanying specification, represents the common and standard practice for reading claims and does not contradict G 1/24.

1.5.2 For a skilled person, it is immediately apparent that the medium removed by an outlet via a continuous outlet is removed at a flow rate, irrespective of whether this is explicitly stated.

The application (page 11, lines 8 to 15) further states that the medium leaving the reactor via the second outlet has the same as or a different flow rate to the medium leaving via the first outlet.

On page 11, lines 8 to 15, the application does not specify a flow rate or a more specific relationship concerning the flow rates since the statement "with the same or a different flow rate" does not impose any limitation but covers all possible combinations.

1.5.3 Therefore, the omission of a reference to flow rates in claim 1, as generally addressed on page 11, lines 8 to 15 of the application, does not extend beyond the original disclosure.

1.6 The disclosure on page 11, lines 8 to 17 of the application is further supported by the specification relating to the chemostat reactor on page 6, lines 22 to 30; Example 2; Figure 1 of the application; and, for example, on page 31, lines 20 to 21.

1.7 Analogous reasoning applies with respect to claim 14.

1.8 The Board therefore considers that the ground for opposition pursuant to Article 100(c) EPC does not prejudice the maintenance of the patent.

2. Main request - sufficiency (Article 100(b) EPC)

2.1 To establish insufficiency of disclosure, the burden of proof is upon an opponent to establish that a skilled person, **using their common general knowledge**, would be unable to carry out the invention (see Case Law of the Boards of Appeal of the EPO, 11th edn., 2025, II.C. 4.1).

The appellant's argument based on T 575/05 and T 817/11 that a lack of guidance cannot be overcome by drawing on common general knowledge is therefore not convincing. The case law cited by the appellant relates

to exceptional cases. For example, in T 575/05, specific conditions had to be selected from various known options without the required guidance for determining a given parameter. Hence, the cited case law is not relevant to the case at hand.

2.2 The appellant argued that the patent did not disclose a working example according to the invention. Example 2 did not demonstrate that the required high cell density was achieved under chemostat conditions as explicitly defined by the final feature of claim 1 ("wherein the cell density in the bioreactor during the fermentation **reaches** at least 5 million cells per ml medium").

The Board does not agree.

2.2.1 Example 2 of the patent repeats the chemostat process of Example 1 in a bioreactor equipped with one outlet containing a separation device allowing impurities with a size below the size of the product and medium to be removed while retaining the product in the bioreactor and a second outlet for harvesting the product. Fermentation starts in a fed-batch mode until the cell density reaches 30 million cells/ml. "Thereafter HD chemostat operation is initiated and the feed is split between harvest and waste [...] to ensure constant cell density" (see page 30, first paragraph).

The appellant has not provided any reason why the skilled person cannot rework Example 2, particularly performing the described chemostat process.

2.2.2 The appellant argued that Example 2 did not explicitly disclose whether any cells or impurities were removed

via the second outlet for harvesting the product during fermentation.

However, a patent application is directed to a skilled person. Example 2 discloses that the product is harvested during the chemostat fermentation process and therefore implicitly discloses to the skilled person that cells and impurities are removed via the second outlet. No disclosure to the contrary is provided by Example 2.

The appellant did not demonstrate why the skilled person would be unable to initiate the fermentation in a fed-batch mode and, after the intended cell density such as 30 million cells/ml has been reached, run the reactor subsequently under chemostat conditions, as disclosed in Example 2.

Instead, the appellant argued that Example 2 (and the patent as a whole) did not disclose how to reach the cell density during the chemostat processing mode and that Example 2 did not represent the method according to claim 1.

2.2.3 However, the Board considers that a skilled person would not interpret claim 1 as requiring the cell density to be reached during the chemostat fermentation process because a chemostat process is characterised by a constant cell density (see the various documents submitted by the parties: D5 (Figure 5), D12 (Chapter 2.2 on page 5) and D14a (Chapter 12.3, second paragraph)).

2.2.4 According to this common understanding of a skilled person, the chemostat fermentation process is controlled so that the growth rate of the microorganism

is equal to the dilution rate, i.e. fresh medium is continuously added while liquid containing unused nutrients, metabolic products and cells are continuously removed at the same rate to keep the culture volume of the reactor, the cell density in the reactor and the harvest rate constant.

2.2.5 The patent does not contain any disclosure implying that the expression "chemostat fermentation process" as referred to in claim 1 has to be interpreted differently from the commonly accepted meaning, a meaning that is confirmed by paragraphs [0006] and [0021] as well as by Example 2 of the patent.

It follows that a skilled person does not expect it to be possible, or even defined by claim 1, to reach a high cell density by using a chemostat fermentation process also during the initial starting phase of the fermentation process.

Rather, from the final feature of claim 1, a skilled person understands that the cell density can well be reached during the initial starting phase of the process, i.e. during the fed-batch and perfusion starting phase of the fermentation process, as exemplified in Example 2. The skilled person also understand that the process defined by claim 1 refers to the subsequent chemostat process in which this high cell density is maintained in a physiological steady state. In line with the respondent's view, the skilled person thus interprets the final feature of claim 1 as "wherein the cell density in the bioreactor during the fermentation **in the chemostat process is** at least 5 million cells per ml medium".

2.2.6 Therefore, the Board considers that Example 2 of the patent illustrates an example of how the process according to claim 1 can be reworked.

2.3 The following further arguments of the appellant constitute mere allegations.

- The cell density would decrease during the high density chemostat fermentation process.
- The patent did not contain any proof that a density of at least $5x10^6$ cells/ml, in particular $30x10^6$ cells/ml, was reached in Example 2.
- The patent lacked guidance on how the cell number could be retained in the bioreactor vessel to make it credible that also the claimed cell density of $5x10^6$ cells/ml could be maintained.

The appellant has not provided any verifiable facts (see Case Law of the Boards of Appeal of the EPO, 11th edn., 2025, II.C.9.1) why the skilled person would not be in a position to rework Example 2 and variations of the process as defined in claim 1 over the whole scope of protection.

2.4 Moreover, the respondent correctly pointed out that Example 2 discloses the following in paragraph [0106]:

"productivity per bioreactor volume of 0.69 g/L day. The specific productivity is 23 PCD"

The term "PCD" refers to picogram per cell per day, see e.g. D3 page 8, lines 15 to 16:

"'Specific productivity' of the cells is the amount of a given biological substance produced per cell per time unit and is usually expressed in pg $cell^{-1}day^{-1}$."

Therefore, the productivity disclosed in Example 2 indirectly provides an indication of the cell density since the cell density can be calculated using the results in paragraph [0106] of the patent:

productivity per ml volume divided by the productivity per cell gives the number of cells per volume, i.e. the cell density (30 million cells/ml)

This corresponds to the cell density at initiation of the HD chemostat operation given in paragraph [0105], lines 8 to 11 of the patent.

2.5 By reference to Case Law of the Boards of Appeal of the EPO, 10th edn., 2022, II.E.1.3.4b, the appellant also argued in relation to Example 2 of the patent that the disclosure of a patent was limited to subject-matter that could be derived directly and unambiguously from it and did not extend to what might be obvious to the skilled person or what might result from an intellectual process performed by the skilled person.

However, this cited case law relates to the allowability of amendments and is not relevant for sufficiency, which also requires considering the common general knowledge.

2.6 Furthermore, no substantiated proof has been provided that the chemostat fermentation process would not be suitable for high cell densities.

Rather, D14a (page 353, second paragraph, last sentence) confirms that the skilled person is aware that high-density cultures can be used in a chemostat process.

On page 369, line 8 from the bottom, D14a further illustrates that a chemostat process can be run at a high cell density of $5x10^8$ cells/ml.

The opponent has argued that the numbers given on page 369 were from a purely hypothetical example and thus of little evidence. However, the numbers are given in a textbook entitled "Practical Fermentation Technology" in a chapter comparing the chemostat process with batch processes for a particular application (the study of the kinetics of mutation, selection and evolution) and citing scientific publications in this context. The Board sees no reason why the numbers given on page 369 should be disregarded.

2.7 To address the argument in point II.3.1 on page 4 of the contested decision that the cell density levels recited in claim 1 "appear to be routinely reached (D6/ D14)", the appellant further referred to D5 and D6.

The appellant argued that D5 and D6 provided verifiable facts that cast serious doubt on whether the skilled person could rework the process of claim 1.

The Board does not accept this view of the appellant.

2.7.1 The appellant's argument concerning D5 is based on the finding reported in D5 that a typical culture of hybridoma cells grown in chemostat mode under the conditions described in D5 reaches a cell density of no more than $3x10^6$ cells/ml as cells are continuously washed out of the bioreactor (see Figure 5A of D5).

This argument is not convincing.

D5 is a research article on a fermentation process involving a particular cell type (hybridoma cells). The skilled person knows that it is not possible to reach a high cell density with any cell type and under all possible process conditions. Therefore, the results obtained for the hybridoma cells under specific conditions and tested in D5 do not give rise to any doubts that the process of claim 1 can be reworked by the skilled person when using cell cultures under appropriate conditions for which it is well known to obtain a cell density of at least 5 million cells per ml medium.

2.7.2 Moreover, D5 describes a standard chemostat process, whereas claim 1 of the patent defines a process that involves removing impurities and medium during the fermentation via the separation device connected to the first outlet.
Therefore, D5 does not provide evidence that the cell density as defined in claim 1 cannot be obtained using hybridoma cells and the process according to claim 1.

2.7.3 The appellant's further argument that the process according to claim 1 could be run under the conditions of a conventional chemostat process, such as that described in D5 (by using a negligible flow rate for the first outlet having a separation device according to claim 1), in which case the claimed high cell density would not be reachable, such that the invention was not sufficiently disclosed over the whole scope of the claim, is also not convincing. This is because the invention as defined in a claim must be evaluated in a technically sensible manner (see Case Law of the Boards of Appeal of the EPO, 11th edn., 2025, II.C.5.4 b)).
What is claimed is a HD chemostat process, not a process run essentially as a classical chemostat

process (as in Example 1 of the patent), and this is not in accordance with the invention.

2.8 D6 relates to a perfusion fermentation process (see claim 1 of D6) and does not demonstrate that the chemostat fermentation process according to claim 1 of the patent cannot be used for a culture medium with a cell density higher than 5 million cells/ml medium.

In fact, D6 demonstrates that high cell densities can be achieved within the experimental routine of a skilled person during the conventional initial starting phase in the bioreactor (see paragraphs [0009], [0010] and [0052] of D6), even before, in the case of D6, the perfusion fermentation process starts (see paragraph [0053] and claim 1 of D6).

2.9 The arguments presented above for the process according to claim 1 apply analogously to the process according to claim 14 of the patent.

2.10 The additional argument that the process of claim 14 could not be reworked since cell fermentation could not take place in the second bioreactor without adding cells is also not convincing. It is immediately apparent to a skilled person that the second bioreactor needs to contain cells. This can easily be achieved by using the further inlet for cells as specified explicitly for the first bioreactor in claim 14, feature vii and as disclosed in paragraph [0019] of the patent or by adding the product containing cells.

The appellant also argued that a skilled person might need to consider several additional alternatives not disclosed in the patent.

This argument is also not convincing because it is not required that a patent describe any possible variations or options that might theoretically exist. Rather, an invention is sufficiently disclosed if at least one way of carrying it out is clearly indicated to a person skilled in the art (see Case Law of the Boards of Appeal of the EPO, 2025, 11th edn., II.C.5.2).

Moreover, in the current case, the skilled person has at their disposal a large number of conceivable alternatives for running the claimed processes, in particular with respect to the products, the cells or microorganisms and the process conditions to be used, such as flow rates, control substrate, culture medium and pH (in line with G 1/03, point 2.5.2 of the Reasons).

2.11 The Board therefore considers that the ground for opposition pursuant to Article 100(b) EPC does not prejudice the maintenance of the patent as granted.

3. Main request - novelty (Articles 100(a)/54 EPC)

3.1 Claim 1 defines a method for producing a product in a bioreactor **in** a high-density chemostat fermentation process.

In the Board's view, the wording of claim 1 does not allow for the interpretation proposed by the appellant according to which the process could be performed under any arbitrary conditions in a bioreactor that has to be merely suitable for being used in a chemostat fermentation process. In fact, the wording of claim 1 does not define that the process takes place in a bioreactor **for** a high-density chemostat fermentation process but rather requires that it take place in a

bioreactor **in** a high-density chemostat fermentation process.

Therefore, the appellant's interpretation is contrary to the wording of claim 1 and the patent's overall consistent teaching. Hence, it is not in line with established case law, in accordance with which the skilled person should try, with synthetical propensity, i.e. building up rather than tearing down, to arrive at an interpretation of a claim which is technically sensible (see Case Law of the Boards of Appeal of the EPO, 11th edn., 2025, II.A.6.1).

3.2 In the following assessment of novelty, the Board interprets claim 1 according to its wording as referring to a method in a bioreactor **in** a high-density chemostat fermentation process, i.e. under chemostat process conditions.

Although claim 1 does not explicitly require a steady physiological state or a constant cell density, the Board considers these features to be considered implicit by a skilled person when interpreting the expression "chemostat fermentation process" in its commonly accepted sense (see the various documents submitted by the parties: D5 (Figure 5), D12 (Chapter 2.2 on page 5) and D14a (Chapter 12.3, second paragraph)). This understanding was even confirmed by the appellant in point 4.2 of the statement of grounds of appeal.

According to this common understanding of a skilled person, the chemostat fermentation process is controlled so that the growth rate of the microorganism is controlled to be equal to the dilution rate, i.e. fresh medium is continuously added while liquid

containing unused nutrients, metabolic products and cells are continuously removed at the same rate to keep the culture volume of the reactor, the cell density in the reactor and the harvest rate constant (as set out above in point 2.2.4). This results in a static physiological environment.

3.3 Novelty in general in view of D1 to D4

3.3.1 The appellant argued (without detailed substantiation, see points 4.1 to 4.2 of the statement of grounds of appeal) that the methods disclosed in D1 to D4 were suitable for the chemostat fermentation process according to claim 1.

This argument is not convincing since claim 1 is directed to a method and not to a bioreactor.

3.3.2 In line with established case law, if a claim concerns an apparatus that differs from a known apparatus only in terms of its indicated use without implying any modifications to allow such use, this use is not an apparatus feature. This means that two apparatuses (differing only in intended use) are considered identical in terms of their structure.

However, if the claim is for a method, as in the case at hand, the situation is not comparable. In such cases, the use feature is a functional method feature comparable in category with the other features (steps) of the method (see Case Law of the Boards of Appeal of the EPO, 11th edn., 2025, I.C.5.2.5).

Therefore, the mere potential suitability of the bioreactors of D1 to D4 for a chemostat fermentation process is insufficient to demonstrate that the claimed

subject-matter, i.e. the claimed process, lacks novelty.

More specifically, documents D1 to D4 do not disclose all the method steps as defined in claims 1 and 14 as discussed below.

3.4 Novelty in view of D1 and D2

3.4.1 D2 is the priority document for D1. Both documents were published before the priority date of the granted patent.

In the following, the Board will focus by way of example on D1. However, in line with the submissions from both parties, the same arguments apply to both D1 and D2.

3.4.2 D1 discloses a process for producing a biopolymer in a continuous perfusion fermentation process where the cell density in the bioreactor reaches at least 10 million cells per ml medium (see claim 1).

The bioreactor addressed by claim 1 of D1 comprises two outlets:

(i) an impurity filter unit which allows impurities to be removed **while retaining cells** and the biopolymer of interest in the bioreactor

(ii) the product harvest module which allows the biopolymer of interest and impurities to be removed **while retaining cells** in the bioreactor

Accordingly, the process for producing a biopolymer according to D1 comprises the following steps:

b) during the fermentation, impurities are removed via

the impurity filter

c) during the fermentation, the biopolymer of interest is harvested via the product harvest module

The process according to claim 1 of D1 is therefore carried out as a perfusion fermentation process, i.e. under conditions in which cells are not removed via the outlet for harvesting. This teaching is confirmed throughout the description of D1 (see, for example, page 2, line 30 to page 3, line 3 and page 4, lines 16 to 21) and in all the examples of D1, where the medium "perfuses" out through the product filter (which according to claim 1 of D1 is again configured to keep the cells in the bioreactor) during the fermentation process.

3.4.3 In contrast, the process of claim 1 of the patent requires cells to be constantly removed via the second outlet having a product harvest module (see method step a) of claim 1). For this reason alone, the subject-matter of claim 1 is novel over D1.

This difference between the subject-matter of claim 1 and the disclosure of D1 also reflects the fundamental distinction between a chemostat fermentation process (cells are constantly removed, the physiological environment remains static) and a perfusion fermentation process (cells remain in the bioreactor), in line with the common understanding of the skilled person.

3.4.4 The appellant argued that in the process according to D1, a further additional outlet ("bleed") was used (see page 2, lines 27 to 28; page 14, lines 15 to 20 and page 16, lines 27 to 28 of D1) and that therefore the process according to D1 also encompassed the continuous

removal of cells from the bioreactor via the bleed outlet during fermentation, as required by claim 1 of the patent. At the same time, the process would take place at steady state (see page 17, line 6; page 18, lines 9 to 12 and 17 to 19; page 19, line 23 and page 20, line 12 of D1).
Therefore, the process according to claim 1 of the patent would simply be a modified perfusion process - a retention-based perfusion process - that is merely labelled as a chemostat process. In other words, even though the patent gave the claimed process a different name, it was, however, in substance a process as disclosed in D1.

This argument is not convincing.

3.4.5 A skilled person immediately recognises that the perfusion process of D1 is in a steady state once the maximal possible cell density has been reached, i.e. when the growth and the mortality rates of the cells are equal.

However, this type of steady state does not correspond to a physiologically static environment, such as aimed for in a chemostat process. In this case, the system reaches a steady state at a growth rate (e.g. controlled by a limiting nutrition) equivalent to the set dilution rate. This equilibration determines the concentration of the cells (see paragraph [0021] of the patent and point 3.2 above).

3.4.6 D1 discloses in the description of the state of the art on page 2, lines 20 to 28 that the product may be harvested continuously via a bleed.

This disclosure in D1 is not presented in the context of the invention of D1, nor in combination with the details of the process according to D1. Hence, the process of D1 is not further characterised by the bleed as disclosed on page 2, lines 20 to 28, nor does D1 on its own disclose a process according to claim 1.

3.4.7 On page 14, lines 15 to 17, D1 further discloses that the reactor may also comprise a bleed via which "'whole' medium comprising both polypeptide of interest and cells" may be taken out. This can be either used for further downstream purification of the product of interest or discarded.

However, D1 does not disclose that the bleed is removed continuously under chemostat conditions ("in a chemostat fermentation process", i.e. in a static physiological environment), i.e. where the feed rate of new medium equilibrates the medium removed during the bleeding (see method step a) of claim 1 of the patent: "new medium is added to replenish nutrients consumed by the cells or microorganisms and to equilibrate the medium removed during removal of impurities and harvesting the product"), keeping the physiological environment and the number of cells in a steady state.

3.4.8 On page 16, lines 20 to 28, D1 further refers to the bleed in the initial starting phase of the fermentation process. It discloses that the permeate bleed rate and the feed rate may be adjusted according to the level of accumulating impurities.

However, D1 does not disclose that the feed rate equilibrates the medium removed during the bleeding or that the physiological environment and the number of

cells is at a steady state during this initial starting phase.

3.4.9 Therefore, the combination of features defined in claim 1 of the patent is not directly and unambiguously derivable from the general disclosure in D1.

3.4.10 The appellant further argued that the examples in D1 disclosed a process in a static chemical environment.

However, the examples of D1 do not disclose product removal via a continuous bleed. On the contrary, they explicitly disclose that product removal occurs via the product harvest module.

Hence, the examples of D1 also do not disclose the process of claim 1 of the patent in which the product, cells, impurities and medium are removed via the product harvest module in a chemostat fermentation process.

3.4.11 The subject-matter of claim 1 is thus novel over D1. As stated above, the same arguments apply to D2.

3.5 Novelty in view of D3

Example 3 (see page 17 ff and Figure 5) of D3 compares fed and fed-batch processes (processes C1 and C2) with a process according to the invention of D3 (process C3) in which a perfusion step is carried out using a hollow fibre membrane (from General Electric) operated in ATF flow mode with an ATF-2 system (from Refine Technology) to retain the cells and the product in the reactor.

3.5.1 In process C3 of Example 3, cell culture is removed at a rate of 10% of the working volume per day above

$10x10^6$ cells $mL^{-1}$ and at a rate of 30% of the working volume per day when the viable cell density exceeds $30x10^6$ cells $mL^{-1}$ (see the paragraph bridging pages 18 and 19). It is therefore immediately apparent that the overall process is not run as a chemostat process since the cell density is not kept constant but increases from $10x10^6$ cells $mL^{-1}$ to $30x10^6$ cells $mL^{-1}$.

3.5.2 The appellant argued that the process of D3 was a chemostat process as in claim 1 of the patent because the process of D3 also reached a steady state (see page 7, lines 21 to 24 and claim 9) at which cell removal was achieved via a bleed (see page 19, lines 23 to 26 of D3).

This argument is also not convincing.

3.5.3 The statement on page 7 of D3 does not imply that the process of D3, in particular process C3 of Example 3, is carried out under chemostat process conditions in which the chemical environment is kept static, not only the concentration of one component of the cell culture medium as suggested in D3. Rather, the conditions are chosen such that the cell growth rate and/or the productivity of the cells is not limited.

Moreover, D3 does not disclose that the bleed is continuously removed under chemostat conditions (i.e. "in a chemostat fermentation process", that is in a physiological steady state), i.e. that the feed rate of the new medium equilibrates the amount of medium removed via the bleed (see method step a) of claim 1 of the patent: "new medium is added to replenish nutrients consumed by the cells or microorganisms and to equilibrate the medium removed during removal of impurities and harvesting the product").

Moreover, the steady state referred to in the perfusion process according to D3 does not correspond to a physiologically static environment in the sense of a chemostat process, as discussed above in point 3.4.5 regarding the disclosure of D1.

Furthermore, Figure 5 of D3 (see below) further demonstrates that the cell densities are not at a steady state in the sense of a chemostat process but rather vary.

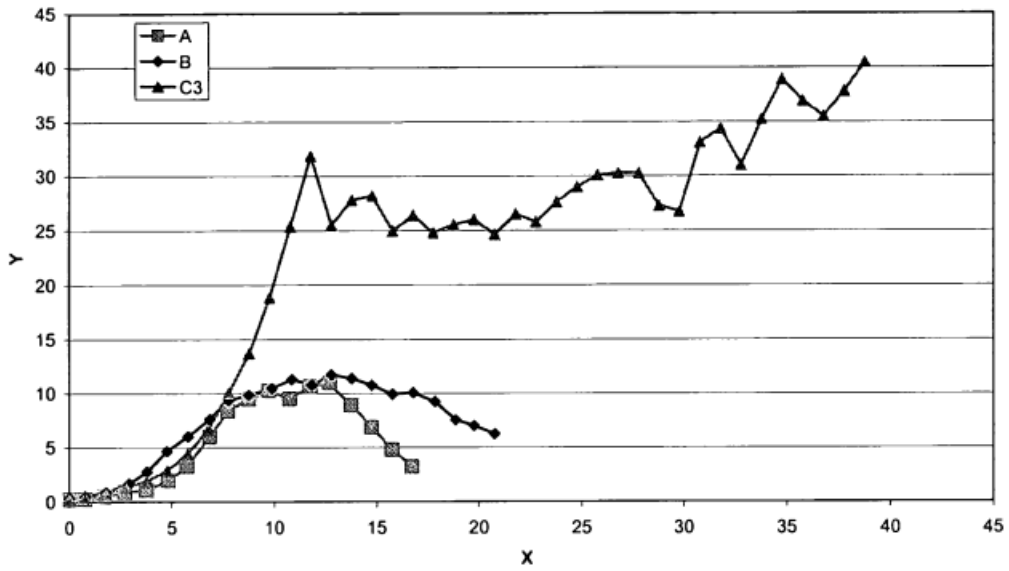


Figure 5 of D3

During the oral proceedings before the Board, the appellant argued for the first time that the process C3 ran under chemostat conditions in particular between days 16 and 23 as the variation in cell density (see Y-axis in Figure 5 of D3) corresponded to that in a chemostat process as shown in Figure 5 of D5.

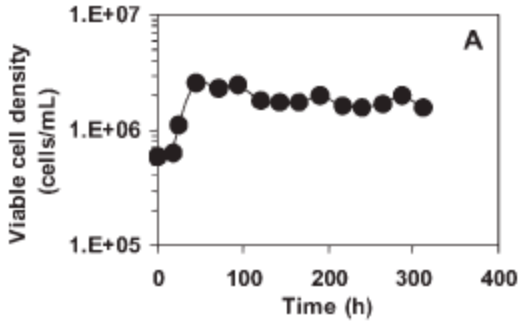


Figure 5 of D5

This argument is *prima facie* not convincing since the scaling of the two graphs in D3 and D5 differs drastically (D3: linear, D5: logarithmic).

The Board therefore did not admit the late-filed new argument already for this reason (Article 13(1),(2) RPBA).

3.5.4 In view of the above, the Board concluded that the subject-matter of claim 1 is novel over D3 and differs from the process C3 of Example 3 of D3 in that:

- the fermentation process is a "chemostat fermentation process" (physiological environment and cell density is kept static during the fermentation process, i.e. microorganisms/cells are grown in a physiological steady state)
- "new medium is added to replenish nutrients consumed by the cells or microorganisms and to equilibrate the medium removed during removal of impurities and harvesting the product"

3.6 Novelty in view of D4

3.6.1 Similar to D1, D4 relates to a perfusion process for culturing cells (see claim 1 and page 1, lines 5 to 7 of D4).

According to the method of D4, the cells are retained in the bioreactor by a separation device (see page 1, lines 35 to 36). Additional biomass removal may be carried out continuously or step-wise (see page 5, lines 14 to 17 of D4). Additional cell culture medium is added to compensate for the biomass removal. The feed for adding additional cell culture medium to the cell culture may be merged into the perfusion feed but may also be separate. The rate of addition of the additional cell culture medium to the cell culture will be the same as the biomass removal rate (see page 5, line 33 to page 6, line 3 of D4).

3.6.2 Even when selecting all features according to claim 1 of the patent from the various options presented on page 5 of D4 as argued by the appellant, D4 nevertheless does not disclose that the addition of culture medium is carried out under chemostat conditions, in particular to replenish nutrients consumed by the cells or microorganism according to method step a) of claim 1 of the patent, nor that the removal of biomass is done under chemostat conditions, i.e. in a physiological steady state, so that the cell density remains constant.

The subject-matter of claim 1 is thus novel over D4.

4. Main request - inventive step (Article 100(a)/56 EPC)

4.1 The parties agree with the finding in point II.3.1 on page 7 of the contested decision that D3 represents a suitable starting point for the assessment of inventive step.

4.2 The subject-matter of claim 1 differs from process C3 of Example 3 of D3 in that:

- the fermentation process is a "chemostat fermentation process" (chemical environment is kept static during the fermentation process, i.e. microorganisms/cells are grown in a physiological steady state, cell density remains constant)
- "new medium is added to replenish nutrients consumed by the cells or microorganisms and to equilibrate the medium removed during removal of impurities and harvesting the product"

4.3 In a first line of attack, the appellant argued that using a chemostat fermentation process provided no technical effect and was therefore not inventive.

This argument is not convincing since a chemostat process taking place in a fermenter has the effect of obtaining products such as "a biopolymer expressed by a cell, an intracellular or extracellular product produced by a cell or microorganism, a periplasmatic product produced by a cell or microorganism, a cell, or a microorganism" (see paragraph [0029] of the patent).

4.4 In a second line of attack, the appellant argued that using a chemostat fermentation process provided "no technical effect over the whole scope of the claim" but achieved the same effect as the perfusion process disclosed in D3 and was therefore not inventive.

This argument is also not convincing since an alternative manufacturing process for obtaining a similar product is not per se obvious just because it can produce the same type of product.

4.5 In a further line of attack, the appellant argued that starting from D3, the objective technical problem could be regarded as to provide an alternative method for

producing a product in a bioreactor. The appellant concluded that the provision of a mere alternative process lacked an inventive step since the chemostat process was known in the art. Referring to D7 to D11, it further argued that it was common practice to use a bleed outlet or a separation device, for example, to increase the cell density of viable cells and to remove impurities and waste from a bioreactor.

This argument is not persuasive either.

4.6 The perfusion and the chemostat process run at different growth conditions. Since fundamentally changing the process conditions carries the risk of unforeseeable complications, a skilled person would not consider this an obvious modification to provide an alternative fermentation process. The appellant has not provided any substantiated argument why starting from D3 the skilled person not only could but would - despite the required substantial modifications - fundamentally change the process conditions of the perfusion fermentation process of D3 to achieve a **chemostat** fermentation process in which the chemical environment is kept static during the fermentation process, i.e. microorganisms/cells are grown in a physiological steady state.

4.7 The Board therefore considers that the subject-matter of claim 1 is not obvious when starting from D3.

4.8 Regarding D1, D2 and D4, the appellant did not provide a detailed discussion of inventive step but rather stated that the same argument applied starting from the examples in these documents as when starting from D3.

As D1, D2 and D4 also disclose a perfusion process in their examples, the same argument applies as for D3. Therefore, a further separate and additional discussion of inventive step in view of these documents is not required.

4.9 Building upon the argument starting from D3, the appellant finally argued that the subject-matter of claims 6 and 14 lacks an inventive step.

Claim 6 depends on claim 1. Therefore, the subject-matter of claim 6 is not obvious for the same reasons as the subject-matter of claim 1.

Claim 14 refers to a fermentation process in two bioreactors where in one bioreactor the process according to claim 1 is taking place. Therefore, the subject-matter of claim 14 is not obvious for the same reasons as set out for the subject-matter of claim 1.

4.10 In summary, the Board considers that the subject-matter of the claims of the main request is not rendered obvious by the cited prior art.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

C. Spira C. Herberhold

Decision electronically authenticated