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Datasheet for the decision of 1 September 2021

Case Number: T 2254/17 - 3.3.08

Application Number: 11717240.3

Publication Number: 2563904

IPC: C12N5/00

Language of the proceedings: EN

Title of invention:
IMPROVED CELL CULTURE MEDIUM

Patent Proprietor:
Novartis AG

Opponents:
Weiss, Wolfgang
CABINET LAVOIX
UCB Biopharma SRL
F.Hoffmann-La Roche AG

Headword:
Culture medium/NOVARTIS

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(2)
RPBA Art. 12(4)

Keyword:
New experimental evidence - not admitted
All requests - inventive step - (no)

Decisions cited:
T 0335/97, T 1018/02, T 1685/07, T 2418/10, T 0996/12

Catchword:

Europäisches Patentamt
European Patent Office
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Beschwerdekammern

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Case Number: T 2254/17 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 1 September 2021

Appellant: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
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Respondent: (Opponent 4)	F.Hoffmann-La Roche AG 124 Grenzacherstrasse 4070 Basel (CH)
Representative:	Jaenichen, Hans-Rainer Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 August 2017 revoking European patent No. 2563904 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair	B. Stolz
Members:	M. R. Vega Laso
	R. Winkelhofer

Summary of Facts and Submissions

I. European patent No. 2 563 904 with the title "Improved cell culture medium" was granted from the European application No. 11717240.3 which had been filed under the Patent Cooperation Treaty and published as WO 2011/134920 A1 (in the following "the application as filed").

II. Four oppositions were filed based on the grounds for opposition of Article 100(a) in conjunction with Articles 54 and 56 EPC, and Article 100(b) and (c) EPC.

III. In a decision dated 4 August 2017, an opposition division found that the subject-matter of claim 1 of the main request and the "auxiliary request Ma" then on file lacked novelty over document (18). The subject-matter of the claims according to the auxiliary requests 1 to 7 and 1a to 7a were found to lack an inventive step within the meaning of Article 56 EPC. Since none of the requests on file fulfilled the requirements of the EPC, the patent was revoked.

IV. The patent proprietor (appellant) filed an appeal and submitted new experimental and documentary evidence.

V. Opponents 1 to 4 (respondents I to IV, respectively) replied to the appeal. Respondents II, III and IV also submitted new evidence.

VI. Pursuant to their subsidiary request, the parties were summoned to oral proceedings before the board.

VII. In a communication, the board expressed a provisional opinion on the admittance of new evidence into the proceedings, as well as on the respondents' requests for remittal and apportionment of costs. The communication included also comments on substantive issues related to Articles 123(2), 84, 83, 54 and 56 EPC.

VIII. In reply, the appellant withdrew the main request and auxiliary request Ma underlying the decision under appeal, the former auxiliary request 1 becoming the new main request, and the former auxiliary request 1a the new auxiliary request Ma. Previous auxiliary requests 2 to 7 and 2a to 7a were re-numbered as auxiliary requests 1 to 6 and 1a to 6a, respectively.

IX. Claim 1 according to the main request reads:

"1. A process for the production of a recombinant polypeptide comprising culturing mammalian cells in a serum-free and protein-free cell culture medium which is characterized by a molar ratio of sodium to potassium ions of between 10 to 1 and 1 to 1 and by a molar ratio of the total ion concentration to the total amino acid concentration of between 1.9 and 4; and expressing the recombinant polypeptide."

Dependent claims 2 to 10 are directed to variants of the process of claim 1.

X. Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that it includes the feature "wherein the concentration of sodium ions is between 50 and 90 mM", and in that the feature "[characterized] by a molar ratio of the total ion concentration to the total amino acid concentration of between 1.9 and 4"

has been deleted. Dependent claim 3 of the main request has been deleted, a new dependent claim 5 introduced and the remaining claims have been re-numbered.

XI. Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that it includes the additional feature "wherein the concentration of sodium ions is between 50 and 90 mM". Dependent claims 2 to 9 correspond to claims 2 and 4 to 10 of the main request.

XII. Claim 1 of auxiliary request 3 differs from claim 1 of the main request in that the cell culture medium is characterized by a molar ratio of sodium to potassium ions of between 8 to 1 and 6 to 1. Dependent claims 2 to 9 correspond to claims 3 to 10 of the main request.

XIII. Claim 1 of auxiliary request 4 differs from claim 1 of auxiliary request 3 in that includes the additional feature "wherein the concentration of sodium ions is between 50 and 90 mM". Dependent claims 2 to 8 correspond to claims 4 to 10 of the main request.

XIV. Claim 1 of each of the auxiliary requests 5 and 6 differs from claim 1 of, respectively, the main request and auxiliary request 3 in that it includes the additional feature "and wherein the total amino acid concentration is between 40 and 100 mM". Dependent claims 2 to 9 of auxiliary request 5 correspond to claims 2 to 4 and 6 to 10 of the main request. Dependent claims 2 to 8 of auxiliary request 6 correspond to claims 3, 4 and 6 to 10 of the main request.

XV. The auxiliary requests Ma and 1a to 6a differ from, respectively, the main request and auxiliary requests 1

to 6 in that the process of claim 1 comprises culturing CHO cells.

XVI. The respondents did not make any further substantial submissions in writing.

XVII. Oral proceedings were held on 1 September 2021 in the presence of all parties.

XVIII. The following documents are cited in the current decision:

(1): WO 2006/026445 A1, published on 9 March 2006;

(18): US 2006/0148074 A1, published on 6 July 2006;

(23): US Patent No. 5,871,999, published on 16 February 1999;

(46): US Patent No. 5,135,866, published on 4 August 1992;

(48): US 2007/0190057 A1, published on 16 August 2007;

(55): Calculation of the Na/K ratio of the medium of D18 using a concentration factor of 27.63;

(60): Exhibit 5, filed on 28 April 2017;

(65): Exhibit 7, filed on 28 April 2017;

(66): Experimental report "Supporting experiments for European Patent EP 2 563 904 B1: Replacement medium preparation", dated 14 December 2017;

(67): Certificate of Analysis for L-Glutamin solution, Sigma-Aldrich;

(68): Experimental report "Supporting cell culture experiments for European Patent EP 2 563 904 B1", dated 14 December 2017; and

(69): Table "Relevant Compounds of the Suspension Medium according to Table 1 of D18".

XIX. The submissions of the appellant, as far as they are relevant to the present decision, were essentially as follows:

Admission and consideration of documents (66) and (68) in the proceedings – Article 12(4) RPBA 2007

Documents (66) and (68) were filed together with the statement of grounds of appeal. Their admittance into the proceedings was subject to Article 12(4) RPBA 2007. Document (66) described the preparation of a culture medium according to document (18). This document did not explicitly disclose the total sodium ion concentration in the culture medium, let alone a molar ratio of sodium to potassium ions. The calculations submitted by the respondents in opposition proceedings were not accurate and did not demonstrate that the information in relation to media components provided in document (18) led to the molar ratio specified in claim 1. The experimental data in document (66) did not represent a fresh case, but confirmed the appellant's argument that document (18) did not describe a culture medium having the molar ratio of sodium to potassium ions (in the following "Na^+/K^+ ratio") specified in claim 1. The data were *prima facie* relevant and decisive for the outcome of the case. In the

communication sent with the summons to oral proceedings, the opposition division had indicated that a finding of lack of novelty must be based on certainty rather than probability, but it had not suggested that experimental evidence from the patent proprietor would be required. The burden of proof on novelty lay on the opponents. Under these circumstances, document (66) was to be admitted into the proceedings.

Document (68) was submitted in reaction to the finding of lack of inventive step in the decision under appeal. In the summons to oral proceedings, the opposition division had indicated that any allegation that a particular technical problem is not solved had to be substantiated by verifiable technical facts. Although the opponents had not provided any additional evidence in this respect, in the decision under appeal the burden of proof was shifted to the patent proprietor. In the absence of an indication from the opposition division as to the relevance of the documents on which the opponents had based their numerous attacks, the patent proprietor had not been able to provide comparative experiments for every document. Comparing different media was not trivial and an exact comparison to the medium described in document (18) had not been possible. The experimental data in document (68) supported the appellant's argument that high viable cell densities and high titters were achieved by the process defined in claim 1. Hence, document (68) should be admitted into the appeal proceedings.

Article 54 EPC – novelty

The opposition division correctly found that, in view of document (18), the claimed subject-matter was novel.

Article 56 EPC - inventive step

The claimed process was not obvious to a person skilled in the art. The opposition division was wrong in finding that document (18) was the closest state of the art because this document was absolutely silent with respect to both the molar Na^+/K^+ ratio and the total ion to total amino acid ratio, and did not address the same problem as the claimed invention. Document (46) or document (1) was a more appropriate starting point for the assessment of inventive step. Starting from either document, the claimed process was not obvious to a person skilled ion the art.

Document (18), which related to the optimization of serum-free mammalian cell culture media for the production of a recombinant protein, described two types of cell culture media, a suspension medium and a replacement medium. Hence, there were at least two starting points for the assessment of inventive step. For both culture media, there was neither an explicit reference to any sodium ion to potassium ion ratio, nor sufficient information for calculating this ratio. Moreover, document (18) did not explicitly disclose a total ion to total amino acid ratio. The opposition division correctly held that the composition of the CD CHO medium used in Examples 7 to 14 of document (18) was not clearly defined. The description of the replacement medium was incomplete and inconsistent. In opposition proceedings, the opponents had submitted theoretical calculations of the molar Na^+/K^+ ratio on the basis of the list of ingredients in Table 2 of document (18). However, these calculations significantly underestimated the actual molar ratio

because several additional sodium sources contributed to the Na^+ concentration and thus to the molar ratio.

The replacement medium described in document (18) differed from the medium used in the process of claim 1 in that it had a molar Na^+/K^+ ratio of 13.6, and a total ion to total amino acid ratio of 8.82, both values being clearly outside of the ranges specified in claim 1. The examples of the patent showed that the technical effect associated with those ranges was a high product titter, with good viabilities and viable cell densities. As apparent from Figures 5A, 5B, 8A and 8B of document (18), cell density and titter achieved by the process described in this document were much lower than those of the claimed process. Thus, the problem to be solved was the provision of an improved cell culture medium for an improved process of production of a recombinant protein.

Starting from document (18), the skilled person did not have any incentive to reduce the molar Na^+/K^+ ratio and total ion to total amino acid ratio in the culture medium, but rather to increase these ratios up to the normal values in other culture media known in the art. The skilled person would not have combined the teachings of document (18) and document (23). Document (23) did not disclose any culture medium composition, let alone a culture medium having a molar Na^+/K^+ ratio as in claim 1. There was no motivation to combine the teachings of documents (18) and (23) because a skilled person seeking to improve product titter would immediately recognize that the teachings of document (23) were not directed to an improvement of protein expression, but to the prevention of cell aggregation, and that the problem of cell aggregation was already solved in the process of document (18) by

using dextran sulphate (see paragraph [0229]). The teachings of document (23) were obscure, in particular as regards the molar ratio of the total ion concentration to the total amino acid concentration, because neither medium composition nor experimental results were provided.

Auxiliary requests 1 to 6, Ma, or 1a to 6a
Article 56 EPC – inventive step

Starting from document (18), the skilled person had no motivation to combine the teachings of this document with those of other documents on file, in particular document (23) or document (48). Document (18) taught away from the invention as claimed in auxiliary requests 1, 2, 4, 1a, 2a and 4a because it suggested the addition of dextran sulphate, which was a sodium source. This would result in a further increase of the sodium concentration in the culture medium which was already above the range specified in claim 1 of those requests.

XX. The relevant submissions by the respondents can be summarized as follows:

Admittance and consideration of the present main request and auxiliary requests 1 to 6, Ma and 1a to 6a in the opposition proceedings

The findings on the admittance and consideration of the auxiliary requests in the decision under appeal should be reversed. The opposition division had failed to consider the principle that auxiliary requests submitted to overcome objections to the main request, particularly if filed shortly in advance of the oral proceedings, should be converging. The submission of a

large number of requests represented an abuse of procedure.

Admittance and consideration of documents (66) and (68) in the appeal proceedings – Article 12(4) RPBA 2007

Documents (66) and (68) should not be admitted into the proceedings because they were filed late and lacked relevance. Document (66), which allegedly reproduced the replacement medium on the basis of the instructions provided in paragraphs [0131] to [0137] of document (18), could have been filed in opposition proceedings in response to the notices of opposition. The calculations of the molar Na^+/K^+ ratio in the replacement medium of document (18), which were submitted by the opponents in the notice of opposition as well as in documents (55), (60) and (65), had not been contested by the appellant in opposition proceedings, even though their relevance was clear from section 14.3 of the communication attached to the summons for oral proceedings before the opposition division. Document (66) could not be regarded as an accurate reproduction of the protocol in document (18). Major deviations from the protocol, in particular additional pH adjustment steps influenced the Na^+ concentration and, consequently, the molar Na^+/K^+ ratio.

Document (68) could and should have been submitted in opposition proceedings. Since it was not plausible from the application as filed that the problem of providing an improved process for the production of a recombinant polypeptide was solved by the alleged invention, the post-published experimental evidence in document (68) could not be taken into consideration. In any case, the data provided in that document did not demonstrate a

technical effect associated to the feature(s) purportedly distinguishing the claimed process from the closest state of the art. The experimental design in document (68) differed from that in the examples of the application in several respects.

Main request
Article 54 EPC - novelty

In the patent at issue, the term "serum-free and protein-free" characterized a chemically defined medium without additives from an animal source (see paragraph [0029] of the patent). Since components like recombinant insulin from a non-animal source (i.e. from bacteria) were not excluded from the culture medium specified in claim 1, document (1), in particular "Medium 12" containing Nucellin™ was novelty-destroying for the claimed subject-matter.

Article 56 EPC - inventive step

Document (18) disclosed a process for the production of a recombinant polypeptide in which mammalian cells were cultivated in a replacement medium characterized by a molar Na^+/K^+ ratio of 9.76 (see document (60)). The process of claim 1 differed from that disclosed in document (18) in that the molar ratio of total ion concentration to the total amino acid concentration in the culture medium was between 1.9 and 4, whereas in the replacement medium this parameter was 8.8.

There was no evidence on file for any technical effect attributable to the distinguishing feature. The examples in the patent were not reproducible and did not show any improvement in comparison to the prior art. Hence, starting from document (18) the problem to

be solved was the provision of an alternative process for the production of a recombinant polypeptide. The solution proposed in claim 1 was obvious to a skilled person in view of the teachings of document (23) or document (1).

Auxiliary requests 1 to 6, Ma, or 1a to 6a
Article 56 EPC – inventive step

Since no technical effect attributable to the feature(s) distinguishing the subject-matter of these requests from document (18) had been demonstrated, the additional features were an arbitrary choice. Hence, the subject-matter of these requests did not involve an inventive step.

XXI. The appellant requests that the decision under appeal be set aside and the patent be maintained on the basis of a main request or of one of auxiliary requests 1 to 6, Ma, or 1a to 6a, filed as, respectively, auxiliary requests 1 to 7 and 1a to 7a on 8 June 2017.

XXII. All respondents request that the appeal be dismissed and document (68) not be admitted and considered in the proceedings. Respondents I, III and IV request that also documents (66), (67) and (69) not be admitted and considered in the proceedings. Respondents I and IV request that, if documents (66) to (69) were admitted and considered, the case be remitted to the opposition division. Additionally, respondent I request not to admit and consider in the appeal proceedings the auxiliary requests filed on 8 June 2017, and respondent IV requests apportionment of costs in case of remittal.

Reasons for the Decision

Admittance and consideration of the present main request and auxiliary requests 1 to 6, Ma and 1a to 6a in the opposition proceedings

1. The present main request and the auxiliary requests 1 to 6, Ma, or 1a to 6a are identical to, respectively, the auxiliary requests 1 to 7 and 1a to 7a underlying the decision under appeal. These requests were filed on 8 June 2017 to preplace a previous version submitted together with the patent proprietor's reply to the opposition division's communication attached to the summons to oral proceedings. The admittance of the new requests was discussed with the parties at the oral proceedings and, for the reasons given in sections 31 and 36 of the decision under appeal, the opposition division decided to consider them.

2. Respondent I’s request not to admit and consider these auxiliary requests in the appeal proceedings cannot be granted, for the following reasons.

3. First, since the auxiliary requests at issue were part of the opposition proceedings, they are also part of the appeal proceedings (Article 12(4) of the Rules of Procedure of the Boards of Appeal (RPBA 2007), which by virtue of Article 25(2) RPBA 2020 applies to the current case). Secondly, under the circumstances of the current case, in particular in the light of the numerous lines of attack on novelty and inventive step put forward by the opponents, not only in their notices of opposition but also at a later stage of the opposition proceedings, the submission of rather numerous auxiliary requests is no abuse of procedure, contrary to respondent I's view. The requests were submitted two months prior to the oral proceedings

before the opposition division, within the time period fixed pursuant to Rule 116 EPC, and only a minor amendment to a claim dependency, which was introduced in response to an objection raised by one of the opponents, was made shortly before the oral proceedings. As the opposition division stated in section 36.3 of the decision under appeal, the auxiliary requests could not have taken the opponents by surprise, because the amended claims included only features already present in the dependent claims of the patent as granted.

4. Lastly, the board does not share respondent I's view that the opposition division, when exercising its discretion, failed to consider the criterion that claim sets filed shortly before the oral proceedings should be converging. While such a criterion has been applied by certain Boards of Appeal in deciding whether a plurality of claim sets filed for the first time in appeal proceedings are admitted and considered by the board (see, e.g., decision T 1685/07 of 4 August 2010), it is questionable whether converging claim sets can be regarded as an absolute requirement for allowing amendments in examination or opposition proceedings (see decision T 996/12 of 14 March 2013, point 6.2 of the Reasons). In any case, it is apparent from the fourth sentence in section 36.3 of the decision under appeal that the opposition division considered non-converging claim sets to be justified in view of the numerous novelty objections raised by the opponents based on different documents.

Admittance and consideration of documents (66) and (68) in the appeal proceedings – Article 12(4) RPBA 2007

5. Pursuant to Article 12(4) RPBA 2007, the board has the discretionary power to hold inadmissible evidence which could have been presented in the first instance proceedings.

6. Together with the statement of grounds of appeal, the appellant submitted document (66) which purportedly provides experimental evidence that the molar ratio of sodium to potassium ions (in the following "molar Na+/K+ ratio") in the culture medium described in paragraphs [0128] to [0137] of document (18) does not fall within the range specified in claim 1 of the requests on file. The respondents opposed to the admittance of this document into the proceedings, arguing, inter alia, that it was filed late and lacked any relevance.

7. In their notice of opposition, the present respondents II and IV cited document (18) to substantiate an objection of lack of novelty and included a calculation of the molar ratio of sodium to potassium ions in the replacement medium as described in paragraphs [0131] to [0137] and Table 2 of document (18). In the reply, the present appellant contested the calculations arguing, inter alia, that it is not possible to derive beyond reasonable doubt the molar Na+/K+ ratio of the replacement medium of document (18) because additional sources of Na+ allegedly not included in the opponents' calculations need to be considered.

8. In the communication attached to the summons to oral proceedings, the opposition division indicated that, as regards the novelty of the subject-matter of the main request then on file, an issue to be decided was "... whether D18 provides without any doubt a medium that has the envisaged Na/K ratio" (see last sentence

of the first paragraph on page 6). The opponents submitted further calculations for which the issues raised by the patent proprietor were taken into account (see documents (55), (60) and (65)).

9. The patent proprietor did not react to this new evidence and, being asked by the opposition division during the oral proceedings whether they had any objections regarding the opponents' calculations, it was confirmed that "... he had no objections regarding the calculations" (see last sentence in section 6 of the minutes of the oral proceedings posted on 4 August 2017). This is reflected on page 15, lines 16 and 17 of the decision under appeal ("The calculations done by the Os[opponents] were not challenged by the P[proprietor]").

10. In view of the circumstances outlined above, document (66) could and should have been presented in opposition proceedings, at the latest in response to the calculations provided by the opponents in documents (55), (60) and (65). The arguments put forward by the appellant fail to persuade that it was not possible to file document (66) in opposition proceedings. Hence, document (66) could not be considered in the proceedings.

11. Document (68) was submitted by the appellant as evidence that the problem of providing an improved process for the production of a recombinant polypeptide was solved by the process defined in claim 1. An objection in this respect had been raised already in each of the notices of opposition of the present respondents.

12. The appellant did not put forward any cogent reasons which may justify the submission of document (68) for the first time in appeal proceedings. The appellant's argument that comparative tests could not be produced for each of the numerous documents cited by the opponents is not persuasive. Since in the communication in preparation of the oral proceedings the opposition division pointed to documents (18) and (46), which were considered to represent the closest state of the art (see second paragraph in section 15.3 of the communication), comparative tests for at least these two documents could and should have been presented in opposition proceedings.

13. Contrary to the appellant's view, an advantageous technical effect allegedly attributed to particular features of the claimed subject-matter distinguishing it from the closest state of the art has to be demonstrated by the patent proprietor (see, e.g., decision T 355/97 of 5 July 2000, point 2.5.1 of the Reasons; and decision T 2418/10 of 3 November 2011, point 3.4 of the Reasons). This applies especially if, as in the present case, none of the examples in the patent shows any improvement whatsoever attributable to a molar Na+/K+ ratio and/or a molar ratio of the total ion concentration to the total amino acid concentration in the particular ranges specified in claim 1.

14. In view of the above, document (68) could not be admitted into the appeal proceedings.

Main request

Rule 80 EPC and Articles 123(2)(3) and 84 EPC

15. The present main request corresponds to the auxiliary request 1 underlying the decision under appeal. The opposition division's findings on Rule 80 EPC and Articles 123(2)(3) and 84 EPC (see sections 31.3, 32 and 33 of the decision) were not contested in the appeal proceedings.

Article 54 EPC – novelty

16. In the decision under appeal, the subject-matter of the claims of auxiliary request 1 was considered novel in view of document (1) which in the opposition division's view did not describe a "protein-free" medium (see section 34.3 and first paragraph on page 12 of the decision). Respondent IV contested this finding.

17. The opposition division was correct in finding that a person skilled in the art does not regard the "Medium 12" described in document (1), which contains NucellinTM, as a protein-free medium. Since the term "protein-free medium" has a clear meaning and imparts a credible technical teaching to the skilled person, the description of the invention in the patent cannot be used to give a different meaning to this term (see decision T 1018/02 of 9 December 2003, paragraph 3.8 of the Reasons).

18. Thus, novelty is to be acknowledged.

Article 56 EPC – inventive step

Document (18) as the closest state of the art

19. Document (18), which was regarded by the opposition division as the closest state of the art, describes cell culture media that support in vitro cultivation,

particularly in suspension, of mammalian cells, such as CHO cells, and methods for cultivating mammalian cells in suspension using those media (see Abstract and paragraph [0034]). Document (18) describes two different serum-free media which are referred to as the "suspension medium" and the "replacement medium". Whereas the suspension medium may contain proteins like transferrin or various cytokines (see first sentence in paragraph [0038]), the replacement medium is described as "... a chemically defined, protein-free eukaryotic (e.g. mammalian) cell culture medium [...], which is capable of supporting the growth, in particular the high-density growth of [...] mammalian cells [...] in suspension culture, increasing the level of expression of recombinant protein in cultured cells, and/or increasing virus production in cultured cells" (see first and second sentence in paragraph [0049]). A method of cultivating mammalian cells using the replacement medium is described also in paragraph [0049].

20. Table 2 of document (18) provides a list of the ingredients and their concentration in the replacement media, and paragraphs [0128] to [0136] describe the preparation of concentrated stock solutions of various groups of ingredients which are combined to prepare the medium, following the procedure described in paragraph [0137]. Examples 7 to 14 illustrate a process for the production of β-galactosidase by CHO cells using as culture medium CD CHO medium, which is characterized in paragraph [0182] as a particularly preferred embodiment of the invention of document (18). A person skilled in the art reading document (18) immediately recognises that the reference in paragraph [0182] to "Table I, the particularly preferred embodiment column" must be erroneous, because ingredients and concentrations for a

particularly preferred embodiment of the replacement medium are shown in the fourth column of Table 2 (see also the last sentence in paragraph [0128], and page 23, last two lines in the right-hand column "... the replacement medium of the present invention (CD CHO medium) ...").

21. The process and the replacement medium of document (18) are directed to the same purpose as the process of claim 1, namely the improvement of cell culture media which allow producing recombinant polypeptides at an industrial scale, in particular in a suspension culture. While document (18) mentions reduced cell clumping as an advantageous effect linked to a particular embodiment of the culture medium including a polyanionic or polycationic compound, preferably dextran sulphate (see paragraph [0049], lines 8 to 11 from the bottom), it can be derived from paragraphs [0116] and [0117] that the ultimate purpose of adding an anticlumping agent to the culture medium is to increase the level of recombinant protein expression in the suspension culture by promoting high-density cultivation of single cells, instead of cell aggregates.

22. It was a subject of dispute in both opposition and appeal proceedings whether a person skilled in the art derives from document (18) a process in which mammalian cells are cultured in a medium having a molar ratio of sodium to potassium ions between 10 to 1 and 1 to 1, as required by the present claims. In the decision under appeal, this question was answered in the affirmative (see assessment of novelty of the main request then on file in section 29.6 of the decision under appeal). Consequently, the culture medium used in the process claimed in auxiliary request 1, which is the present

main request, was found to differ from the medium of document (18) (only) in that the molar ratio of the total ion concentration to the total amino acid concentration is within the particular range specified in claim 1.

23. The appellant contested these findings arguing that a skilled reader did not learn from document (18) that the molar Na+/K+ ratio was important. This argument is not persuasive. In the current case, the process using the replacement medium described in document (18) represents, as such, the "starting point" for the assessment of inventive step, i.e. the specific point in the state of the art from which the skilled person sets off to arrive at the claimed invention. The question whether the skilled person derives from document (18) the importance of a particular molar Na+/K+ ratio in the culture medium could be relevant to the assessment of inventive step if, for instance, the technical contribution of the invention were the selection of a particularly advantageous molar Na+/K+ ratio, because without being aware of the importance of this parameter the skilled person would possibly not follow a path leading towards the selection invention. However, since in the present case the objective technical contribution is a particular range for a different parameter (the molar ratio of the total ion concentration to the total amino acid concentration), the question whether or not document (18) teaches the importance of the molar Na+/K+ ratio is immaterial.

24. The appellant alleged that the disclosure of the replacement medium in document (18) was inconsistent and incomplete as regards the pH adjustment steps, volumes to be achieved and required osmolarities, and submitted document (66) in support. This document was

not admitted into the appeal proceedings, pursuant to Article 12(4) RPBA 2007 (see paragraphs 6 to 10 above). The opposition division's findings regarding the alleged inconsistencies in the disclosure of paragraphs [0128] to [0137] and Table 2 of document (18) (see pages 15 and 16 of the decision under appeal) are endorsed by the board. Like the opposition division, the board sees no reason to doubt that the calculations of the molar Na+/K+ ratio of the replacement medium based on the list of ingredients in Table 2 of document (18) (see documents (55), (60) and (65)) are accurate.

The technical effect

25. The opposition division correctly found that the experimental tests in the examples of the application relate to the effect of different temperature profiles (Example 1) combined with a pH shift (Example 2) during the cultivation of cells, on cell density, viability and product titter. While culture media as defined in the present claims are used in the tests, the examples fail to establish a technical effect attributable to a molar ratio of the total ion concentration to the total amino acid concentration within the range specified in claim 1 in the culture medium, let alone a synergistic effect attributable to a combination of this feature with a molar Na+/K+ ratio as specified in claim 1.

26. Moreover, the opposition division correctly found that the technical effect purported in the application cannot be verified by a person skilled in the art, because the application does not provide sufficient information on the CHO clone used in the examples for the production of undefined monoclonal antibodies mAB1 and mAB2.

27. As further correctly found by the opposition division, in the current case a technical effect which is attributable to the specified molar ratio of the total ion concentration to the total amino acid concentration in the culture medium cannot be established by direct comparison of the viable cell density and polypeptide yield apparent from the figures of document (18) with the data provided in the examples of the application as filed. Since culture conditions, CHO clones and expressed polypeptides are different, the data obtained from performing those two processes cannot be compared.

28. Although the technical effect had been an issue from the outset of the opposition proceedings, in appeal proceedings the appellant submitted, for the first time, comparative tests as document (68). However, for the reasons given above in paragraphs 11 to 14, this document was not admitted into the proceedings. Consequently, a technical effect attributable to the features distinguishing the claimed subject-matter from the closest state of the art cannot be established.

The problem solved

29. Consequently, in accordance with the case law of the Boards of Appeal the problem to be solved by the skilled person, starting from the particularly preferred embodiment of the replacement medium described in document (18), is formulated as the provision of a process for the production of a recombinant polypeptide using an alternative serum-free and protein-free culture medium. Undisputedly, the process of claim 1 solves the problem.

Obviousness

30. In the decision under appeal, the claimed subject-matter was found obvious in view of document (18) alone or in combination with either document (1) or document (23). The opposition division held that, while the skilled person did not find in document (18) any hint that motivated them to modify the replacement medium described therein, in the light of the rather unambitious technical problem the skilled person would follow a "try-and-see" approach.

31. The appellant contended that the skilled person was not motivated to modify the replacement medium of document (18) applying the teachings of document (23).

32. For the purpose of reducing cell aggregation in a culture of adherent animal cells, in particular CHO cells, document (23) suggests culturing the cells in a culture medium characterized by a 10:1 to 1:1 molar ratio of total inorganic ions to total amino acids (see, e.g., claim 1 of document (23)). If it were not already part of the common general knowledge in the field of mammalian cell suspension culture for producing polypeptides at an industrial scale, the statements in paragraphs [0116] and [0117] of document (18) made the skilled person aware of the fact that cell aggregation in a suspension culture may have deleterious effects on the level of recombinant protein expression. Contrary to the appellant's view, the fact that document (18) already provides a solution to the problem (adding dextran sulphate to the medium), would not deter the average skilled person seeking to provide an alternative process from applying the clear approach suggested in document (23).

33. For these reasons, it was obvious to the skilled person to modify the process described in document (18) as

suggested in document (23). Since no inventive skills are required to make this modification, an inventive step cannot be acknowledged for claim 1 of the main request.

Auxiliary requests 1 to 6, Ma, or 1a to 6a
Article 56 EPC – inventive step

34. Claim 1 of each of the auxiliary requests includes additional features taken from the dependent claims which specify a narrower range for the molar Na+/K+ ratio (auxiliary requests 3, 4, 6, 3a, 4a and 6a), a particular range for the concentration of sodium ions (auxiliary requests 1, 2, 4, 1a, 2a and 4a), or a particular range for the total amino acid concentration (auxiliary requests 5, 6, 5a and 6a). In the process according to auxiliary requests 1a to 6a, the cultured cells are CHO cells, as described in document (18).

35. Since a technical effect attributable to any of these features or combinations of features has not been established, the solutions provided in each of the auxiliary requests are arbitrary choices from a host of different solutions available to a person skilled in the art. Applying these solutions to solve the problem of providing an alternative process for the production of a recombinant polypeptide in a serum-free and protein-free culture medium does not involve any inventive skills. Thus, an inventive step cannot be acknowledged for the subject-matter of these requests.

Conclusion

36. There is no set of claims on file on the basis of which the patent could be maintained. Questions of remittal or apportionment of costs do not arise.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: On behalf of the Chair (according to Art. 8(3) RPBA 2020):

L. Malécot-Grob R. Winkelhofer

Decision electronically authenticated