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Datasheet for the decision of 12 July 2022

Case Number: T 1831/16 - 3.3.08

Application Number: 12160789.9

Publication Number: 2522717

IPC: C12N5/00

Language of the proceedings: EN

Title of invention:
Oligopeptide-free cell culture media

Patent Proprietor:
Baxalta Incorporated
Baxalta GmbH

Opponents:
CSL Behring GmbH
Dr. Ursula Sprenzel

Headword:
Oligopeptide-free cell culture media/BAXALTA

Relevant legal provisions:
EPC Art. 123(2), 76(1), 54

Keyword:
Amendments - allowable (yes)
Novelty - (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1831/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 12 July 2022

Appellant: (Patent Proprietor 1)	Baxalta Incorporated 1200 Lakeside Drive Bannockburn, IL 60015 (US)
Appellant: (Patent Proprietor 2)	Baxalta GmbH Thurgauerstrasse 130 8152 Glattpark (Opfikon) (CH)
Representative:	Muncke, Nadja Feldmeier, Kaspar Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Appellant: (Opponent 1)	CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg (DE)
Representative:	Ball, Gregory Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Party as of right: (Opponent 2)	Dr. Ursula Sprenzel Rudolfshofer Strasse 17 91207 Lauf a.d. Pegnitz (DE)
Representative:	Zwicker, Jörk Röhlk, Christian ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 June 2016 concerning maintenance of the European Patent No. 2522717 in amended form.**

Composition of the Board:

Chairman B. Stolz
Members: D. Pilat
D. Rogers

Summary of Facts and Submissions

I. European patent No. 2 522 717 is based on European patent application No. 12 160 789.9, entitled "Oligopeptide-free cell culture media", filed as a divisional application of the earlier European patent application No. 07702574.0 (EP 1 974 014) (hereinafter "the parent application", filed under the Patent Cooperation Treaty on 3 January 2007 and published as WO 2007/077217).

II. The patent was opposed on the grounds of Article 100(a), in conjunction with Articles 54 and 56, and of Articles 100(b) and (c) EPC. An opposition division decided, that the main request (patent as granted) extended beyond the content of the application as filed (Article 100(c) EPC), that new auxiliary requests 1 and 2, filed as AR-MRC and AR1c, lacked novelty under Article 54 EPC and did not involve an inventive step under Article 56 EPC, respectively, and that new auxiliary request 3, filed as AR3c, contravened Articles 76, 123(2) and 84 EPC. Finally, the opposition division decided that new auxiliary request 4, submitted during oral proceedings, met the requirements of the EPC.

III. The patent proprietors and opponent 1 (hereafter appellant I and appellant II, respectively) lodged an appeal against the decision of the opposition division.

IV. Appellant I replied to appellant II's statement of the grounds of appeal.

V. Opponent 2 (respondent) replied to appellant I's statement of grounds of appeal.

VI. Oral proceedings took place on 12 July 2022. At the end of the proceedings, the appellant I withdrew all its auxiliary requests.

VII. Claim 1 according to the main request reads as follows:

"1. A method for expressing at least one protein, comprising the steps of:
(a) providing a culture of cells;
(b) introducing at least one nucleic acid sequence comprising a sequence coding for at least one protein selected from the group of coagulation factor VII, coagulation factor VIII, coagulation factor IX, vWF, ADAMTS 13 and furin into the cells;
(c) selecting the cells carrying the nucleic acid sequence; and
(d) expressing the protein in the cells in a protein-free cell culture medium that does not comprise oligopeptides, the cell culture medium comprising at least 0.5mg/L of a polyamine."

Dependent claims 2 to 8 define particular embodiments of the method of claim 1.

VIII. The following document is referred to in this decision:

D4: WO2006/045438 (published 4 May 2022).

IX. The submissions made by **appellant I**, insofar as relevant to the present decision, may be summarized as follows:

Main request (claims 1-8)
Articles 76(1) and 123(2) EPC

The decision under appeal was correct in that claim 1 found a basis in claims 11 to 13 and paragraphs 1, 37 and 40 of the parent application. The combination of features of granted claim 1 could be directly and unambiguously derived from claims 11 to 13 of the parent application. Although each of claims 12 and 13 of the parent application were only dependent on claim 11, the skilled person immediately understood that each of the claims defined a different aspect of the method of claim 11 which could be combined without a selection to be made. The amended method of claim 1 step (d) referring to "a protein-free cell culture medium that does not comprise oligopeptides" was based on paragraph [024] of the parent application.

Novelty (Article 54 EPC)

Document D4 was concerned with media that contain both soy hydrolysate and a polyamine. The addition of polyamine allowed to reduce the amount of hydrolysate, thereby reducing lot-to-lot variability while at the same time increasing productivity (see paragraphs [001], [014] and [016]). One aspect of the invention related to an animal protein-free cell culture medium comprising at least one polyamine and a plant- and/or yeast-derived hydrolysate, in a concentration sufficiently reduced in order to avoid potential inhibitory effects of the hydrolysate (see paragraph [028], emphasis added). Paragraphs [062] and [063] of Example 2 set out how the hydrolysate and a polyamine were used. Their use in different combinations was illustrated in Figures 1 to 5 and Figure 9. These paragraphs constituted the figure legend of Figures 1 to 5 and 9.

(a) Figure 1 compared the volumetric FVIII-CoA productivity and the specific growth rate of GD8/6

cells as a function of the media used for culture, which were supplemented with different lots (K119-1, K138-1, M022963, M024423, M022453) of soy hydrolysates (0.4 % (w/v)).

(b) Figure 2 disclosed a table which compared the volumetric FVIII-CoA productivity of GD8/6 cells grown in media with different soy hydrolysate concentrations.

(c) Figures 3 and 4 disclosed graphs which compared the volumetric FVIII-CoA productivity of GD8/6 cells and the specific growth rates of GD8/6 cells, respectively, as a function of the media used for culture, which were supplemented with different lots of soy hydrolysates (0.25 % (w/v)) (A) in the absence of putrescine and (B) in the presence of 1 mg/L putrescine.2HCl.

(d) Figure 5 disclosed a table which compared the volumetric FVIII-CoA productivity and the specific growth rate of GD8/6 cells and their standard deviation when grown in media with different selected lots of soy hydrolysates 0.4 % (w/v) or 0.25 % (w/v) or with soy hydrolysates 0.25 % (w/v) and putrescine.2HCl at 1 mg/L.

(e) Figure 9 referred to media none of which was oligopeptide-free and comprising polyamine.

All these media comprised hydrolysates and were not oligopeptide-free.

Document D4 did not disclose a medium containing a polyamine without soy hydrolysate. It disclosed a method using a medium supplemented with soy hydrolysate in the range of 0.1 to 1,0% and/or with putrescine at a concentration in the range of 0 to 1mg/L, but without providing a clear and unambiguous disclosure of each and every value of these ranges in combination, let

alone a combination that was unsupported and not in line with the teaching of the patent as a whole.

X. The submissions made by **appellant II**, insofar as relevant to the present decision, may be summarized as follows:

Main request (claims 1-8)
Articles 76 and 123(2) and EPC

Claim 1 of the main request added matter in view of the combination of claims 1, 11, 12 and 13 of the parent application (present as "clauses" 1, 11, 12 and 13 in the patent application as filed on pages 20 to 21). Each of claims 12 and 13 in the parent application was dependent only on claim 11, so that claim 1 created a combination of features that was not present in the parent application as filed. The relevant features concerning the medium were defined separately from those of the method.

The "oligopeptide-free" feature was referred to in the specific context of the embodiment of the cell culture medium (e.g. paragraph [012]). This paragraph did not mention methods of expressing proteins, let alone a set of proteins as recited in claim 1(b). The method disclosed in paragraphs [0037] and [0040] did neither refer to the use of an oligopeptide-free medium nor to a specific set of proteins as defined in claim 1(b).

Novelty (Article 54 EPC)

Document D4 was concerned with the expression of proteins in cell cultures. It explicitly referred to methods for expressing at least one protein comprising providing a culture of cells, introducing an exogenous

nucleic acid and selecting the cells according to paragraph [047].

Example 2 of document D4 explicitly referred to the expression of FVIII in cell culture methods with a medium as defined in claim 1 part (d). The cell culture medium used in example 2 was the BAV-medium defined in Example 1 to which varying concentrations of soy hydrolysate in the range of 0,0 to 1,0% and varying concentrations of 0-10 mg/L polyamines could be further added (see paragraph [061]). The medium was protein- and oligopeptide-free and containing at least 0.5 mg/L of a polyamine, as the constant feed of BAV medium was supplemented with soy hydrolysates in the range of 0,1-1,0% and/or addition of putrescine.2HCl in the range of 0-1 mg/L (see paragraphs [062] and [063]). The conjunction **"or"** linking the soy hydrolysate and the polyamine explicitly disclosed a culture medium comprising polyamine without the additional presence of soy hydrolysate.

XI. The submissions made by the **respondent** (Opponent 2), insofar as relevant to the present decision, may be summarized as follows:

Main request (claims 1-8)
Article 76(1) EPC

The parent application did not explicitly disclose the method steps (b) and (d) recited in claim 1 in combination.
Claim 12 specified that the medium in step (d) was an oligo-peptide free medium according to claim 1, while claim 13 specified that the protein of step (b) was selected from the group of coagulation factor VII, coagulation factor VIII, coagulation factor IX, vWF,

ADAMTS13, and furin. The paragraphs [0037], [0038] and [0040] of the parent application corresponded to the features of claims 11 to 13.
Since there was neither an indication that these different embodiments had to be combined nor that claims 12 and 13, each solely dependent on claim 11, had to be combined, the combination of features of present claim 1 required the skilled person to make a plurality of selections offending against Article 76(1) EPC.

Novelty (Article 54 EPC)

Document D4 referred to methods for expressing at least one protein especially to methods comprising the step of providing a culture of cells, introducing an exogenous nucleic acid and selecting the cells as specified in (a) to (c) of paragraph [047]. Example 2 disclosed specifically the expression of factor VIII in CHO cells (see paragraphs [062], [063]).
In paragraph [0063] of Example 2 the cultures were supplied with BAV-medium as defined in Example 1 without supplementation of soy hydrolysate and polyamines, or supplemented with soy hydrolysate in the range of 0.1-0.4% and/or putrescine.2HCl, ornithine.HCl, and spermine.4HCl in the range of from 0-18 mg/L (equivalent to 0-10 mg/L of the polyamine without .HCl) (emphasis added). Hence, document D4 explicitly disclosed four possible combinations of compounds in the protein-free and oligopeptide-free medium:

(i) no soy hydrolysate and no polyamines,
(ii) soy hydrolysate,
(iii) soy hydrolysate and putrescine, ornithine, and spermine,
(iv) putrescine, ornithine, and spermine.

The skilled person could therefore clearly and unambiguously derive from paragraphs [061] to [063] in document D4 " a medium with a polyamine and without a hydrolysate" that fell within the scope of the claims. Despite the absence of any experimental results, there were no "serious doubts" which substantiated that the skilled person could not reproduce the medium in accordance with document D4 and thereby inevitably arrive at a result falling within the scope of claim 1. Reference was made to decision T 230/01.

The Figure legends were provided in paragraphs [019] to [027] of document D4.

XII. The appellant I requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request.

XIII. The appellant II and the respondent requested that appellant I's appeal be dismissed and the patent be revoked.

Reasons for the Decision

Main request (claims 1-8)
Articles 76(1) and 123(2) EPC

1. The granted patent results from a divisional application of the earlier parent application EP 07702574.0 (EP 1 974 014). The claims of the parent application are included as "clauses" in the description of the divisional application (cf. paragraph [0071| of the patent application). It follows that if the subject-matter of the claims of the patent

lacks a basis in the patent application, it also lacks a basis in the parent application.

2. Appellant II and the respondent argued that there was no direct and unambiguous disclosure for a method comprising steps (b) and (d) set out in claim 1 in combination.

3. The board notes that claim 12 of the parent application refers to a method of claim 11 which explicitly refers to the use of the oligopeptide free medium according to claim 1 of the parent application. The entire list of proteins to be expressed in claim 1 step (b) is disclosed in the context of a method for expressing at least one protein (see paragraphs [037] and [040] and claim 13 of the parent application). Hence, the parent application discloses that the features characterizing the medium are also intended to characterize the medium used in the method for expressing a recombinant protein (see paragraphs [012] to [016] and paragraphs [17-33] and [34-44] of the parent application). Thus, the combination of features of granted claim 1, especially part (b) and (d), have a direct and unambiguous basis in the parent application. Claim 1 therefore complies with the requirements of Articles 76 EPC and 123(2) EPC.

Article 54 EPC

Document D4

4. Appellant I contended that one object of the invention disclosed in document D4 was to reduce plant and/or yeast derived hydrolysate to overcome inhibitory effects affecting the recombinant production yield by adding polyamine.

Although the term "and/or" in Example 2 of document D4 disclosed apparently a method using a medium containing putrescine but no soy hydrolysate, a more detailed analysis of the experiments and of the corresponding figures showed that none of the media contained only polyamine and no soy hydrolysate. Thus, the "and/or" reference in the section describing some experiments did not reflect what was done and what was actually disclosed in an enabling way. A disclosure could only be prejudicial to novelty if it was also enabling. Besides, the reference to two ranges was not a clear and unambiguous disclosure of each and every value of these ranges - even less so in combination with each other.

5. First, the board accepts that document D4 primarily relates to a method for expressing a recombinant protein in cells which are cultivated in an animal protein free medium comprising both polyamines and a plant- and/or yeast hydrolysate.

5.1 Secondly, document D4 discloses in Example 2 cell cultures of recombinant mammalian cells (e.g. CHO-cells stably expressing Factor VIII = GD8/6 cells) which were grown in suspension. Since, in order to be reproduced by the skilled person, the CHO-cells stably expressing Factor VIII require first a step of selecting the cells having been transformed and having integrated the nucleic acid sequence in their genome, the method described in document D4 must implicitly comprise steps (a) to (c) defined in the method of claim 1. In a further step, the culture of these cells in BAV medium was supplied with a constant feed of BAV medium supplemented with soy hydrolysates in the range of 0,1-1,0% and/**or** addition of putrescine.2HCl in the range of 0-1 mg/L (cf. Figure 1-5).

Hence, the method of expressing recombinant FVIII may explicitly be carried out in BAV medium supplemented with either soy hydrolysate **or** putrescine.2HCl or alternatively with soy hydrolysate **and** putrescine.2HCl.

5.2 Even if example 2 does not report any experiments of culturing cells for the production of recombinant proteins using a medium comprising polyamines and no soy hydrolysate, the disclosure in a prior art document is not confined to the specific working examples, but comprises any reproducible technical teaching described therein (see Case Law of the Boards of Appeal of the European Patent Office, Ninth Edition July 2019, page 121, last full paragraph; decision T 12/90, reasons 2.11). In other words, subject-matter which is explicitly disclosed in a prior art document but not exemplified cannot be dismissed as non-existent.

According to the established case law, the relevant question is not whether the skilled person actually had carried out each and every embodiment disclosed in the prior art document but rather whether the disclosure is sufficient to enable the skilled person, in combination with its common general knowledge, do so.
The need for an enabling disclosure is in conformity with the principle expressed in Article 83 EPC, which principle applies with equal force to both a prior art document and a patent.

5.3 Since appellant I provided no evidence that the method in example 2 of document D4 could not be performed, they failed to discharge their burden of proof, with the consequence that their unfounded allegations cannot be taken into account by the board.
Absent any evidence to the contrary, the board is satisfied that the skilled person is able to carry out

the method of culturing GD8/6 cells in suspension for the production of recombinant factor VIII using a medium comprising polyamines and no soy hydrolysate as explicitly disclosed in example 2 of document D4.

5.4 Although paragraphs [062] and [063] in example 2 of document D4 refer to two ranges of concentrations of soy hydrolysate and putrescine.2HCl, the skilled person was not required to select a specific combination from the ranges of concentrations assigned to soy hydrolysate and to putrescine, as the method of expressing recombinant FVIII is explicitly disclosed to be carried out in BAV medium supplemented with either soy hydrolysate **or** putrescine.2HCl or alternatively with soy hydrolysate **and** putrescine.2HCl.

It follows that only the last option above requires multiple selections from two lists of equally preferred alternative concentrations, whilst the second option does not. Thus, a skilled person, choosing the second option from these three alternatives, would have inevitably supplemented the cell culture BAV medium with putrescine at 1 mg/L. It is established case law that the upper limit of a concentration range explicitly discloses said value. This finding is also reached when the same considerations are applied to the disclosure of the CHO clone GD8/6 cultured in suspension in a BAV medium supplemented with putrescine at 18 mg/L (see paragraph [063] of example 2).
As a method of expressing recombinant FVIII carried out in a BAV-medium supplemented with putrescine at a concentration of 0 mg/L results in no putrescine being added, which contradicts the addition of putrescine that characterises the second option, said method is only disclosed in a BAV-medium supplemented with either putrescine at a concentration of 1 mg/L or with

putrescine.2HCl, ornithine.HCl, spermine.4HCl at a concentration of 18 mg/L.

5.5 Even if one were to argue that the second option in paragraph [062] required a selection from the concentrations encompassed by the range of 0 to 1 mg/L, only one single selection would be needed.

6. Since, the method described in document D4 anticipates the method of claim 1, the main and sole request lacks novelty (Article 54 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated