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Datasheet for the decision of 29 June 2021

Case Number: T 1465/15 - 3.3.08

Application Number: 10004392.6

Publication Number: 2213724

IPC: C12N5/02, C12N7/02, C12N1/16, C12N1/20

Language of the proceedings: EN

Title of invention:
Animal protein-free media for cultivation of cells

Patent Proprietor:
Baxalta Incorporated
Baxalta GmbH

Opponents:
F. Hoffmann-La Roche AG
GE Healthcare Bio-Sciences AB

Headword:
Method for cell cultivation/BAXALTA

Relevant legal provisions:
EPC Art. 76(1), 123(2), 56
RPBA 2020 Art. 13(2)

Keyword:
Main request, Auxiliary Requests 1 and 2 - added matter (yes)
Auxiliary request 3 - requirements of the EPC met

Decisions cited:
T 1253/07, T 1621/16, G 0002/10

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1465/15 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 29 June 2021

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 12 May 2015 revoking European patent No. 2213724 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 2 213 724 is based on European patent application No. 10004392.6, - a divisional application of the earlier European patent application No. 05798575.6 (EP 1 805 298) (hereinafter "the parent application" filed under the Patent Cooperation Treaty on 12 October 2005 and published as WO 2006/045438 on the 4 May 2006) - and was opposed on the grounds of Articles 100(a), in conjunction with Articles 54 and 56 EPC, 100(b) and (c) EPC. An opposition division considered the main request and auxiliary requests AR3, AR4, AR7 and AR8 to AR11 to contravene Article 56 EPC, and auxiliary requests AR5 and AR6 to contravene both Articles 84 and 56 EPC. The patent was revoked.

II. The patentee (appellant) lodged an appeal. With its statement of grounds of appeal, it submitted a main request and auxiliary requests 1 to 31. With a letter dated 28 May 2021, it submitted a new main request and auxiliary requests 1 to 11 (corresponding to previous AR6 to AR9 (including the correction submitted on 15 June 2020), AR17 to AR20 (including the correction submitted on 15 June 2020), and AR28 to AR31 (including the correction submitted on 15 June 2020)).

III. Opponent O1 (respondent) replied to the statement of grounds of appeal and filed Exhibit A. In reply to the respondent's response, appellant filed further submissions.

IV. Opponent O2 (respondent II) did not reply to the statement of grounds of appeal and did not attend the oral proceedings, as announced in writing.

V. Oral proceedings took place on 29 June 2021.

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

"1. A method for expressing a target protein, comprising the steps of:
a) growing a culture of cells in an animal protein-free cell culture medium, the culture medium comprising putrescine and soy hydrolysate, wherein the putrescine is present in the culture medium in a concentration ranging from 0.5 to 10 mg/L and the soy hydrolysate is present in a concentration ranging from 0.05 % (w/v) to 1 % (w/v);
b) introducing a nucleic acid sequence comprising a sequence coding for the target protein into the cells;
c) selecting the cells carrying the nucleic acid sequence; and
d) selectively inducing the expression of the target protein in the cells,
wherein the target protein is at least a biologically active part of a blood coagulation factor."

Independent claim 5 relates to a method of producing an animal protein-free cell culture medium of claim 1.

Dependent claims 2 to 4 are particular embodiments of the method of claim 1.

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

D3: WO 01/23527 (published on 5 April 2001);

D5: EP 0481791A2 (published on 22 April 1992);

D11: Igarashi K. and Kashiwagi K. "Polyamines:

Mysterious Modulators of Cellular Functions." Biochemical and Biophysical Research Communications; vol. 271(3), pp. 559-64, 19 May 2000;

D13: Eun Jung Kim, *et al.* "Development of a Serum-Free Medium for the Production of Humanized Antibody from Chinese Hamster Ovary Cells Using a Statistical Design." In Vitro Cellular & Developmental Biology - Animal, vol. 34, no. 10, pp. 757–761, 1998;

D15: Quest International data sheet for "HyPep 1510" of March 2000;

D18 WO 98/08934 (published on 5 March 1998);

D25: Y. H. Sung, *et al.* "Yeast hydrolysate as a low-cost additive to serum-free medium for the production of human thrombopoietin in suspension cultures of Chinese hamster ovary cells." Applied Microbiology and Biotechnology, vol. 63 (5) pp. 527-536, 2004;

D33 Schlaeger, E.-J. *et al.* "SF-1, A LOW COST CULTURE MEDIUM FOR THE PRODUCTION OF RECOMBINANT PROTEINS IN BACULOVIRUS INFECTED INSECT CELLS." Biotechnology Techniques, vol. 7 (3), pp. 183-188, 1993.

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

Main request (claims 1-5)
Articles 123(2) and 76 EPC

Both the parent application claims 1 and 4 and items 1 and 4 in [0078] of the patent application read:

> "1. An animal protein-free cell culture medium, comprising at least one polyamine and at least one protein hydrolysate derived from the group consisting of plants and yeast."

and

> "4. The animal protein-free cell culture medium according to claim 1/item 1, wherein the polyamine is putrescine in a concentration ranging from about 0.5 to about 10 mg/L, and the protein hydrolysate is soy hydrolysate in a concentration ranging from about 0.05 % (w/v) to about 5 % (w/v)."

Paragraph [0032] of the parent and of the patent application read:

> "In a preferred embodiment the total concentration of the plant- and/or yeast-derived protein hydrolysate in the animal protein-free cell culture medium is about 0.05 % to about 5 % (w/v), more preferably about 0.05 % to about 2 % (w/v), more preferably about 0.05 % to about 1 % (w/v), more preferably about 0.05 % to about 0.5 % (w/v), most preferably about 0.05 % to about 0.25 % (w/v); i.e. if the medium contains a plant- and a yeast derived protein hydrolysate, the total concentration is calculated by the summing up the concentration values of each of the protein hydrolysate components contained in the medium."

Thus, the patent disclosed five preferred soy hydrolysate concentration ranges with only the upper concentration of these ranges being reduced.

Basis for producing the medium of claim 1 by adding a polyamine and a hydrolysate to a basal medium was described in paragraphs [0034], [0042], [0061] and [0062].

Eventually, the method for expressing a target protein using a culture medium according to the invention was disclosed in paragraph [0047], while the blood clotting factor was derivable from the paragraph [0049] and from the example of the patent. Paragraph [0049] pointed towards in particular Factor VIII used in examples 2, 5 to 9 and 12 of the patent. The claimed target protein was derivable from item 14 in paragraph [0078].

Thus, the patent application clearly pointed to a method of expressing a target protein in paragraph [0047] being at least a biologically active part of a blood coagulation factor which used an animal protein-free medium according to the invention, as illustrated in the majority of the examples. The animal protein-free media used was clearly disclosed in item 4 of the patent application except that the soy hydrolysate component was selected from the list of concentration ranges disclosed in paragraph [0032].

The method of producing an animal protein-free cell culture medium of claim 5 was implicitly disclosed in paragraphs [0034], [0016], [0018] of the patent application describing a basal medium, as illustrated in example 1, optionally comprising auxiliary substances, and which embraced the addition of putrescine and of protein hydrolysate.

Decision T 1253/07 of 15 December 2010 item 2.3 supported appellant's view that two elements described

in separate lists of compounds and in several examples could be combined without introducing added matter, if the link between them was clearly established and highlighted.

Thus, decisions T 1253/07 of 15 December 2010 and T 1621/16 of 14 October 2019 established that under certain circumstances highlighted elements from different lists of some length might be brought together without offending the requirements of Article 123(2) EPC.

The case underlying decision T 1621/16 concerned a dishwashing detergent composition defined in claim 1 of the main request by several elements each defined by % by weight of the total composition ranges. These amended ranges were reported to differ from original claim 1 in that they concerned one or only a subgroup of a larger group of elements and were in % by weight more limited. Thus, the amendments introduced in claim 1 were based on multiple selections from lists of converging alternatives (i.e. lists of options ranked from the least to the most preferred, wherein each of the more preferred alternatives is fully encompassed by all the less preferred and broader options in the list), and should not be treated like selections from lists of non-converging elements (i.e. mutually exclusive or partially overlapping alternatives) (see item 1.4 of the reasons). The multiple selections from lists of converging alternatives ought therefore to be analogous to the deletion of elements from lists.

If the amendments were based on multiple selections from lists of converging alternatives, it had to be assessed whether the specific combination resulting from the multiple selections was supported by the

content of the application as filed to conclude that the requirements of Article 123(2) EPC were met. To this end two conditions had to be met:

- i) the combination should not be associated with an undisclosed technical contribution, that is, no unwarranted advantage should be derived from linking the specific combination of more and less preferred alternatives to an inventive selection which is not supported by the application as filed; and
- ii) the combination should be supported by a pointer in the application as filed. Such pointers can be provided by the example(s) (as in decisions T 27/16, Reasons, point 13.10; and T 615/95, Reasons, point 6, last paragraph) or by specific embodiment(s) of the application, as this/these generally represent(s) the most detailed and preferred form(s) of the invention.

The combination of features selected from lists of converging alternatives resulted in the subject-matter of claim 1.

Hence, the subject matter of claim 1 was directly and unambiguously disclosed in the patent application. The main request complied with Articles 123(2) and 76 EPC.

Auxiliary requests 1 and 2
Articles 123(2) and 76 EPC

Auxiliary request 1 differed from the main request in that the method of producing an animal protein-free cell culture medium of claim 5 was deleted.

Auxiliary request 2 differed from the main request in that the method of producing an animal protein-free cell culture of claim 5 was deleted and the blood coagulation factor was Factor VIII.

No arguments other than those submitted for the main request were put forward.

Admission of auxiliary request 3 into the proceedings – Article 13(2) RPBA 2020

Auxiliary request 3 corresponded to a corrected version of auxiliary request 9 where claim 1 was limited to CHO cells and claim 2, referring to mammalian cells, insect cells, avian cells, bacterial cells and yeast cells, was deleted. Since this issue was raised for the first time in the board's communication and the deletion of dependent claim 2 did not add any complexity to the case or any new issues to the case, admission of auxiliary request 3 into the appeal proceedings under Article 13 RPBA 2007, applicable to the present case in the light of the transitional provisions under Article 25(1) and (3) of the RPBA 2020 was requested, as the summons were issued on 29 October 2019 and re-issued on 20 December 2019, i.e. before the new RPBA came into effect. The deletion was furthermore in line with the requirement of procedural economy and was filed at the first opportunity after the issue was brought to the attention of the patentee.

Auxiliary request 3
Articles 123(2) and 76 EPC

Claim 1 related to a method for expressing a target protein, comprising the steps of: a) growing a culture of cells in an animal protein-free cell culture medium,

the culture medium comprising putrescine and soy hydrolysate, wherein the putrescine is present in the culture medium in a concentration ranging from 0.5 to 10 mg/L and the soy hydrolysate is present in a concentration ranging from 0.05 % (w/v) to 1 % (w/v); ... d) ... wherein the cell/target protein combination is CHO cells/coagulation factor VIII.

The CHO cells/coagulation factor VIII was supported by and highlighted throughout the examples and in paragraph [0051] of the patent application. The skilled person reading the content of the patent application was pointed towards this specific combination without having to rely on item 14 of the patent application.

Figure 2 disclosed that the cell productivity of Factor VIII was measured in culture media comprising soy hydrolysate at a concentration of 0.15, 0.25, 0.4, 0.75, 1.00 (w/v), i.e. ranging from 0.05 % (w/v) to 1 % (w/v). Figures 3, 4 and 9 referred also to a CHO cell/coagulation factor VIII expression system cultured in a medium comprising soy hydrolysate with concentrations ranging from 0.05 % (w/v) to 1 % (w/v).

Thus, claim 1 had a basis in the patent application [0051], [0032], item 14 or in the parent application claim 14.

Article 56 EPC

Document D3 or alternatively document D33 represented the closest prior art for the subject-matter of claim 1.

Document D3 related to an animal protein-free cell culture DMEM/HAM's F12 medium preferably between 1 to 5

g/L corresponding to 0.1% (w/v) to 0.5% (w/v) of soy extract (see page 8, lines 8 to 22). Ultrafiltered soy peptone with an average molecular weight of 350 daltons and a total nitrogen content of approximately 9.5% and a free amino acid content of approximately 13% was advantageously added to said medium (see page 8, lines 23 to 29). The product characteristics of the soy peptone described in document D3 were identical to those of HyPep 1510 as defined in document D15, and was added preferably at 2.5 g/L (corresponding to 0.25% (w/v)) to the medium (see page 18, Table 2, page 22, lines 8 to 11). Example 8 described the culture of recombinant FVIII-CHO cells in a protein-free and serum-free medium containing different hydrolysates in particular a soy hydrolysate at 0.25% (w/v) (see page 22, lines 7 to 11).

Although document D3 disclosed a protein- and serum-free medium comprising soy hydrolysate, there was no disclosure of a medium containing putrescine nor an explicit reference to the "HyPep 1510" soy hydrolysate. The ultrafiltered soy hydrolysate having an average molecular weight of 350 Da and a free amino acid content of approximately 13% was dissimilar to the HyPep 1510 soy hydrolysate described in document D15 comprising 7.3% free amino acids or 12% free amino acids when compared to the content of the overall amino acids in the medium. Likewise the total nitrogen in the medium of document D3 was 9.5 % which is dissimilar to the total nitrogen of 9.0 % disclosed in the HyPep 1510 described in document D15. Even if 57% of oligopeptides in the medium had a molecular weight between 200 to 500 Da, 43% of them had another molecular weight. There was no information about whether the oligopeptides having this molecular weight were symmetrically distributed or not. From these data, it could not be

concluded that the soy hydrolysate used in document D3 was equivalent to the HyPep 1510 from Quest and inherently contained putrescine at a concentration within the range defined in claim 1.

The difference between document D3 and the subject-matter of claim 1 was that the combination CHO cells/ coagulation factor VIII was grown in an animal protein-free cell culture medium, said medium comprising putrescine and soy hydrolysate, wherein the putrescine is present in the culture medium in a concentration ranging from 0.5 to 10 mg/L and the soy hydrolysate is present in a concentration ranging from 0.05 % (w/v) to 1 % (w/v).

The effect underlying the differences was that this method enabled an increased cell specific productivity Q_p and a more consistent productivity in culture (i.e. reducing the lot-to-lot variability) to be achieved.

The technical problem to be solved was therefore the provision of an improved method for expressing CHO/ Factor VIII in an animal protein-free medium.

The solution was the method of claim 1.

There was no motivation, neither in document D3 nor in document D5, to modify and solve the technical problem identified above to arrive at the method of claim 1. The effect in documents D3 and D5 depended on the other components of the medium and could not be assigned only to one element of the medium.

Document D5 described a biochemically defined culture medium for culturing engineered Chinese hamster ovary (CHO) cell lines, which was essentially free from

protein, lipid and carbohydrate isolated from an animal source. The defined media comprised Nucellin, a recombinant form of insulin, which had to be avoided according to the patent paragraph [0035]. It followed that the biochemically defined media of document D5 could not be defined as an animal protein-free cell culture medium according to the patent.
The concentration of 0.16 mg/L of putrescine.2HCl used in example 1 was lower than the amount referred to on page 7, lines 11-14: "... known to play a role in maintaining the structure of the endoplasmic reticulum and to be required by certain CHO cells lines to support growth. Putrescine or a salt thereof is preferably added in an amount 0.01-1.0 mg/L."

Documents D11, D13, D18, D25 provided no evidence of common general knowledge. Document Dll referred to growth and proliferation effects of polyamines in general. Document D13 related to a serum-free medium, wherein the sign *-* in table 1 represented a low amount of the compounds (see page 758, right column, end of third paragraph). Tables 1 and 2 defined serum-free media comprising insulin and transferrin.
Document D18 (not yet mentioned during the written appeal proceedings) related to a serum-free replacement medium comprising insulin and transferrin (see page 67, lines 15 to 19). Document D25 proposed the addition of yeast hydrolysate or soy hydrolysate to serum-free media (SFM) for the production of human thrombopietin in CHO cells and discussed the yeast hydrolysate lot-to-lot variability (see page 534, right column, last paragraph).

Document D33 disclosed two insect cell media. The animal protein-free cell culture medium "IP301" contained a protein hydrolysate (“Yeastolate”) in a

concentration of 0.4% (w/v), 1 mg/L spermidine, 1 mg/L spermine 4HCl (corresponding to 0.581 mg/L spermine) and 1 mg/L putrescine 2.HCl (corresponding to 0.547 mg/L putrescine). The "IP301" medium comprised a protein hydrolysate derived from yeast ("Yeastolate") rather than a soy protein hydrolysate.

The skilled person would not have isolated parts of document D5 from their context to derive technical information which would be distinct from the integral teaching of that document (see Case Law of the Boards of Appeal of the European Patent Office Ninth Edition July 2019, Chapter I.D.9.4, p.246).

Thus, starting from document D3, the skilled person, without a pointer, would not have known how to achieve an increased cell specific productivity and a more consistent productivity in culture (i.e. reducing the lot-to-lot variability). Hence, the solution of claim 1 involved an inventive step.

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

Main request (claims 1-5)
Articles 123(2) and 76 *EPC*

The present patent was granted on a divisional application from EP 05798575. The original claims of the parent application were put as "items" into the description (cf. paragraph [0078] of the divisional application). Hence, if the subject-matter of the opposed claims found no basis in text of the divisional application, then both the requirements of Article 123(2) EPC and 76(1) EPC were not fulfilled.

The method of expressing a target protein comprised the steps of :
growing a culture of cells in an animal protein-free cell culture medium comprising
- (i) a particular concentration range of putrescine, i.e. a concentration range between 0.5 to 10 mg/L;
- (ii) a particular concentration range of soy hydrolysate, i.e. a concentration range between 0.05 % (w/v) to 1 % (w/v); and

wherein the target protein was at least a biologically active part of a blood coagulation factor.

There was no basis for a method of expressing a particular target protein selected from a list of target proteins in combination with the specific medium defined in claim 1 (see paragraph [0049] of the patent application).

Item 4 disclosed a medium comprising a protein hydrolysate which was a soy hydrolysate ranging from 0.05% to 5% (w/v) instead of the claimed concentration ranging from 0.05% to 1%.
The intermediate concentration ranges in paragraph [0032] were all mentioned to be "preferred" but were not assigned to soy hydrolysate. They were assigned to plant- and/or yeast-derived protein hydrolysate in general. The specific and claimed combination of soy hydrolysate in combination with "a concentration range between about 0.05% (w/v) to 1% (w/v)" was accordingly not directly and unambiguously derivable, in an individualized form, from paragraphs [0032] or [0038]. The patent application had no pointer for the preferred use of a medium comprising soy hydrolysate concentration ranging from 0.05% to 1% over any of the other preferred concentration ranges. Since the

examples of the patent used animal protein free media with many different soy hydrolysate concentrations they could not serve either as a pointer for a soy hydrolysate concentration range according to claim 1. A "pointer" in the sense of decision T 1621/16 cannot point towards multiple media containing different concentrations of soy hydrolysate concentration ranges.

Paragraph [0047] of the patent application related to a method of expressing a target protein using an animal protein-free cell culture medium according to the invention.

The target proteins in paragraph [0049] listed a biological part of a blood coagulation factor, such as Factor VIII, a biological part of a protein involved in the production of red blood cells and angiogenesis, such as erythropoietin, or a monoclonal antibody. Likewise, the examples of the patent could not serve as a "pointer" to any particular preference either as they referred to a Factor VIII, a monoclonal antibody or an erythropoietin.

The method claim 5 was based on granted product claim 1 and paragraphs [0034], [0042], [0061] and [0062] of the patent application.
Paragraph [0034] related to a basal medium without any addition of putrescine. Paragraph [0042] related to polyamine concentration ranges and mentioned that said polyamine was selected from the group consisting of cadaverine, putrescine, spermidine, spermine, agmatine, ornithine and combination thereof. There was no pointer that putrescine was the preferred polyamine of all the polyamines listed. Paragraph [0061] related to the preparation of a basal medium containing varying

concentrations of soy hydrolysate in the range of 0.0 to 1.0%.

The specific combination of features of claim 1 was neither explicitly nor implicitly derivable as the clear consequence of what was explicitly disclosed from any of the items and paragraphs recited above. Thus, there was no clear pointer to the claimed combination in the sense of decision T 1621/16.

Hence, claim 1 infringed Article 123(2) EPC.

Auxiliary requests 1 and 2
Articles 123(2) and 76 EPC

The arguments raised against claim 1 of the main request under Articles 123(2) and 76 EPC were applicable and were maintained.

Admission of auxiliary request 3 into the proceedings – Article 13(2) RPBA 2020

The summons to attend oral proceedings were first set on 4 March 2020 for this case and were issued on the 29 October 2019. At the request of the parties and due to the COVID pandemic situation, summons to attend oral proceedings were scheduled for the 15 July 2020 and issued on the 13 December 2019, and re-scheduled for the 29 June 2021 and issued on the 14 August 2020.

Auxiliary request 3 corresponded to auxiliary request 9, submitted with appellant's statement of grounds of appeal, from which claim 2 was deleted, which was submitted in response to a communication under Article 17(2) RPBA 2020. The deletion of claim 2 in auxiliary request 9 was considered to be an amendment to

appellant's appeal case that was made after a notification of a summons to oral proceedings pursuant to Article 13(2) RPBA 2020 and thus was not admissible as it could have been filed earlier.

Auxiliary request 3
Articles 123(2) and 76 EPC

The method of claim 14 of the parent application referred back to claim 1, whereas the method of item 14 of the patent application referred first back to item 12 which was then referring back to item 1. The claims of the parent application were therefore not adopted verbatim and could not provide an adequate basis for the subject-matter of claim 1.

No basis could be found in paragraphs [0032] and [0051] for the subject-matter of claim 1, as there was no direct and unambiguous disclosure in these paragraphs to specifically select a culture medium comprising soy hydrolysate present in a concentration ranging from 0.05 % (w/v) to 1 % (w/v) and to combine it with the specific cell/target protein consisting of CHO cells/ coagulation factor VIII to achieve an expression of a target protein in cells.

The examples in the patent application could neither provide an adequate basis for the claimed subject-matter as examples 10 and 11 related to cell/target protein combinations consisting of BHK cells / erythropoietin, Epstein Barr virus transformed and immortalized human B cells / human antibodies. Furthermore, all examples for the production of a target protein referred to a medium containing soy hydrolysate at a concentration of 0.4% or 0.25% (w/v).

Article 56 EPC

Document D3 or alternatively document D33 represented the closest prior art for the subject-matter of claim 1.

Document D3 disclosed an animal protein-free cell culture DMEM/HAM's F12 medium preferably between 1 to 5 g/L corresponding to a 0.1% (w/v) to 0.5% (w/v) of soy extract (see page 8 lines 8 to 22). Ultrafiltered soy peptone with an average molecule weight of 350 daltons with a total nitrogen content of approximately 9.5% and a free amino acid content of approximately 13% was advantageously added to said medium. The product characteristics of the soy peptone disclosed in document D3 was identical to the ultrafiltered soy hydrolysate "HyPep 1510", i.e. 57.5% of the peptides had a molecular weight ranging from 200 to 500 daltons (i.e. having an average molecular weight of 350 daltons), its total nitrogen content was about 9% and its free amino acid content was about 12%. Moreover, the soy hydrolysate was preferably added at 2.5 g/L (see page 18, Table 2, page 22, lines 8-11). The DMEM/ HAM's F12 medium supplemented with 0.25% (w/v) of soy hydrolysate inherently had to contain 1.48 mg/L putrescine according to the calculation set out in the patent application. In this context, it was referred to decision T 990/09 which considered that the culture medium described in document D3 was anticipated by the medium defined in the data sheet for "HyPep1510" (see document D15). CHO cells as well as factor VIII were particularly preferred or preferred for their cultivation in the medium according to the invention as carried out in example 8 using a culture medium defined in example 4 comprising 0.25% (w/V) of soy hydrolysate (see page 12, lines 1 to 8, example 8 and Table 2).

The soy hydrolysate "HyPep1510" at a concentration of 0.4% (w/v) had a putrescine concentration of 2.24 mg/L (see patent Figure 6). Figure 2 of the patent showed that the addition of soy hydrolysate at concentrations ranging from 0.15% to 0.75% increased the cell specific productivity of factor VIII while at a concentration of 1% it decreased again. The method of claim 1 covered all these embodiments. Figures 5 and 9 of the patent showed only a boosting effect.

In the absence of a control, a synergistic effect in accordance with [0018] of the patent, *beyond the sum of their individual effects,* could not be taken into account (see decision T 0605/14 of 7 June 2018). Figures 3B and 4B of the patent demonstrated that putrescine had at best a boosting effect on the volumetric productivity. Given the scope of claim 1 and the lack of experiments in the patent demonstrating that the technical problem of providing an improved method of expressing a protein using an animal protein-free medium had actually been achieved, the technical problem had to be reformulated in less ambitious terms as the provision of an alternative method of expressing a protein using an animal protein-free medium.

Document D5 described a biochemically defined culture medium for culturing engineered Chinese hamster ovary (CHO) cell lines, which was essentially free from protein, lipid and carbohydrate isolated from an animal source (see abstract), as the use of serum was problematic (see page 2, line 32 to page 3, line 10). It was proposed to improve CHO cell growth by adding putrescine at a concentration of 0.5-1 mg/L and by adding hydrolysates at a concentration of 0.25% (w/v) (see page 7, lines 11 to 14 and lines 32 to 34).

The boosting effect of putrescine on cell growth was established in the art and demonstrated in documents D11 and D13 (see D11, page 559, first sentence of the introduction, page 563 last paragraph; D13 abstract, line 6; Table 3 "Putrescine"). The addition of putrescine to culture media was common too (see document D18, Table II on page 50; document D25, page 528, Table 1; document D33, "IP301" medium).

Document D3 disclosed that the culture of cells in media with serum represented a problem for providing a standardized cell production and standard growth and carried a risk of contamination with unwanted agents (see page 1, lines 13 to 18 and page 2, lines 9 to 20). The solution to this problem was to add soy hydrolysate to the medium (see page 5, lines 6 to 12; page 8, lines 9 to 16 and lines 23 to 29).

Since the patent provided no results which demonstrated that it solved the problem of providing an improved method for expressing CHO/Factor VIII in an animal protein-free medium, across the full breadth of claim 1, the technical problem had to be reformulated to the provision of an alternative method to the one of document D3.

Faced with the technical problem of providing an alternative method of producing Factor VIII in CHO cells, the skilled person would have come across document D5, lying in the same technical field, and would have been motivated to complement the medium with putrescine, known to be boosting CHO cell growth and its protein production, at a concentration up to 1.0 mg/L putrescine to a medium containing a soy hydrolysate and would have arrived at the claimed cell

culture medium with a reasonable expectation of success and without inventive activity.

X. The appellant requested that the patent be maintained on the basis of the new main request or, in the alternative, based on any of auxiliary requests 1 to 3 filed with letter dated 28 May 2021.

XI. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request (claims 1-5)
Articles 123(2) and 76(1) EPC

1. The granted patent is based on a divisional application of the earlier parent application EP 05798575 (EP1805298). The description of both applications is identical. The claims of the parent application were included as "items" in the description of the divisional application (cf. paragraph [0078| of the patent application). It follows that if the subject-matter of the claims lacks a basis in the patent application, it also lacks a basis in the parent application.

2. In accordance with established jurisprudence, the relevant question to be decided in assessing whether or not claim 1 encompasses subject-matter extending beyond the content of the application as filed, is whether the skilled person would derive the subject matter directly and unambiguously from the application as filed.

3. Claim 1 of the main request relates to a method for expressing a target protein, comprising the steps of:

- a) growing a culture of cells in an animal protein-free cell culture medium, the culture medium comprising putrescine and soy hydrolysate, wherein the putrescine is present in the culture medium in a concentration ranging from 0.5 to 10 mg/L and the soy hydrolysate is present in a concentration ranging from 0.05 % (w/v) to 1 % (w/v);
  ...
- (d) selectively inducing the expression of the target protein in the cells,

wherein the target protein is at least a biologically active part of a blood coagulation factor.

3.1 Claim 1 differs from item 4 of the patent application in that the soy hydrolysate is present in a concentration ranging from 0.05 % (w/v) to 1 % (w/v) and in that the target protein is at least a biologically active part of a blood coagulation factor.

3.2 The respondent argued that there was no basis for a method for expressing at least a biologically active part of a blood coagulation factor according to claim 1.

4. Appellant asserted that there was an adequate basis in the patent and the parent application for the subject-matter of claims 1 and 5.

Appellant referred to decisions T 1253/07 of 15 December 2010 and T 1621/16 of 14 October 2019 which held that under certain circumstances highlighted elements from different lists of some length may be brought together without offending the requirements of Article 123(2) EPC.

5. The board is not convinced by the appellant's arguments.

5.1 It is undisputed that the patent application does not explicitly disclose the specific combination of the concentration range of soy hydrolysate and the target protein of claim 1.

5.2 The basic principle underlying Article 123(2) EPC and the ground of opposition under Article 100(c) EPC is that any amendment to a European patent relating to the disclosure (the description, claims and drawings) is subject to Article 123(2) EPC and can only be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the application as filed. This definition has become the "gold" standard for assessing any amendment for its compliance with Article 123(2) EPC (see decisions G 2/10 item 4.3 referring to G 3/89 and G 11/91, points 1, 1.3 and 3 of the Reasons).

5.3 Although a "pointer" to the claimed combination of features resulting from multiple selections by examples may help to determine the disclosure of an application as filed, it is vital to examine whether the claimed combination is directly and unambiguously derivable, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the patent application.

5.4 The claimed concentration range of soy hydrolysate derives from a list of converging alternatives disclosed in paragraph [0032] and the target protein to be expressed is selected from a list of alternatives disclosed in paragraph [0049].

5.5 As regards the presence of a "pointer" to the claimed combination in the patent application, the board cannot share proprietor's view for the following reasons:

5.5.1 First, although the five concentrations ranges recited in paragraph [0032] are presented as more and more preferred, there is no preference derivable from this list which would point to the claimed combination of concentration ranges of soy hydrolysate and putrescine as directly and unambiguously preferred over any of the remaining possible combinations. Furthermore the list in paragraph [0032] relates to plant- and/or yeast-derived protein hydrolysate in the animal protein-free culture medium and not to a soy hydrolysate as claimed.

Even if one accepts that the method of expressing a target protein disclosed in [0047] refers to an animal protein-free medium of the invention as defined in item 4, the skilled person needs first to select a more limited soy hydrolysate concentration range from the list of plant- and/or yeast-derived protein concentration ranges so as to combine it with the concentration range of putrescine disclosed in item 4, and secondly to select "at least a biologically active part of a blood coagulation factor" from the list of target proteins disclosed in paragraph [0047].

5.5.2 Example 2 discloses a method for growing CHO cells stably expressing Factor VIII, named GD8/6 cells, in an animal protein-free medium. The cell culture is supplied with a basal medium BAV, as defined in example 1, known to contain 0.08 mg/L of putrescine, supplemented with either soy hydrolysates in the range of 0.1 to 1.0% and/or putrescine.2HCl in the range of 0 to 1 mg/L, corresponding to a calculated

concentration of putrescine ranging from 0 to 0.5% mg/L (cf. Figure 1-5). Alternatively the cell culture was supplemented with soy hydrolysate at a concentration of 0.25% or 0.4% (w/v) and putrescine.2HCl at a concentration of 3.6 mg/L or 18 mg/L (cf. Figure 9). Finally, examples 5 to 8 disclose the culture of GD8/6 cells in basal medium (BAV) containing 0.4% (w/v) or 0.25% (w/v) of different soy hydrolysate lots or containing different concentrations of soy hydrolysate lot M022257 (in the range of 0.15 - 1.0% w/v) or containing 0.25% (w/v) of soy hydrolysate supplemented with putrescine.2HCl at a concentration of 1 mg/L. Example 12 is directed at the culture of GD8/6 cells in a culture medium supplemented with putrescine.2HCl at concentrations of 3.6 mg/L or 18 mg/L.

5.5.3 All the examples cited above describe the expression of Factor VIII in CHO cells, and not of any other blood coagulation factors, cultured in a medium comprising soy hydrolysate at concentrations of either 0.4% or 0.25% (w/v), except examples 6 and 12.
Example 6 describes the expression of Factor VIII in a basal medium, known to contain a putrescine concentration of 0.08 mg/L, which is supplemented with different concentrations of soy hydrolysate lot M022257 in the range of 0.15 - 1.0% (w/v) corresponding to a putrescine concentration of 0.86 mg/L to 5.75 mg/L.
Example 12 describes the expression of Factor VIII in the same basal medium supplemented with soy hydrolysate at concentrations of 0.0, 0.25 or 0.4% (w/v) corresponding to a putrescine concentration of 1.43 mg/L to 2.24 mg/L.

5.5.4 Thus, even taking into account the examples of the patent application, there is no direct and unambiguous disclosure of the method of claim 1.

5.6 The method of claim 1 extends therefore beyond the content of the application as filed and contravenes Articles 123(2) and 76 EPC.

Auxiliary request 1 (claims 1-4)

6. Auxiliary request 1 differs from the main request in that the method of producing an animal protein-free cell culture medium of claim 5 is deleted.

7. Since the subject-matter of claim 1 was not amended, auxiliary request 1 contravenes Article 76 and 123(2) EPC for the same reasons as for the main request.

Auxiliary request 2 (claims 1-4)

Auxiliary request 2 differs from the main request in that claim 5 is deleted and the target protein is defined to be a biologically active part of factor VIII.

8. Although the subject-matter of claim 1 of auxiliary request 2 was amended to express a target protein, wherein said target protein is a biologically active part of factor VIII, the skilled person had still to select, as stated in point 5.5.1 above, first a more limited soy hydrolysate concentration range from the list of plant- and/or yeast-derived protein concentration ranges to combine it with the concentration range of putrescine disclosed in item 4, and secondly to select from the list of target proteins disclosed in paragraph [0047] "a biologically active part of factor VIII".

Even taking into account the examples 2, 5 to 8 and 12 of the patent application, there is no direct and unambiguous disclosure of the method of claim 1.

9. The board concludes that the amendments to claim 1 of the auxiliary request 2 contravene Articles 123(2) and 76 EPC.

Admission of auxiliary request 3 into the proceedings

10. The appellant argued that auxiliary request 3 was the result of a straightforward deletion of dependent claim 2 carried out in reaction to an objection of clarity raised for the first time in the board's communication under Article 17(1) RPBA. This claim request was filed at the first opportunity after this issue had been brought to the attention of the appellant. The deletion of dependent claim 2 did not add to the complexity of the case nor raise any new issues. It was also in line with the requirement of procedural economy.

10.1 The respondent argued that since summons to oral proceedings were sent in 2020, the Rules of Procedure of the Boards of Appeal 2020 were applicable. In particular Article 13(2) RPBA 2020, which stipulates that "any amendment to a party's appeal case made ... after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned".

10.2 The board considers that auxiliary request 3, consisting of a corrected version of auxiliary request 9 submitted with appellant's statement of grounds of appeal, is a legitimate reaction to the board's communication and intends to address an objection

raised for the first time in the board's communication under Article 84 EPC. Thus, auxiliary request 3, consisting of the corrected version of auxiliary request 9, could not have been filed earlier and does not give rise to new issues, which the board and the parties cannot reasonably be expected to deal with without adjournment of the oral proceedings. Its admission does not run contrary to procedural economy and in view of the exceptional circumstances above is considered to be justified. For these reasons, the board decided to admit auxiliary request 3 into the proceedings.

Auxiliary request 3 (claims 1 and 2)

11. Auxiliary request 3 differs from the main request in that the method for expressing a target protein of claim 1 comprises the steps of ... d) selectively inducing the expression of the target protein in the cells, wherein the cell/target protein combination is CHO cells/coagulation factor VIII. Dependent claims 2, 3 and independent claim 5 have been deleted.

Articles 123(2) and 76(1) EPC

12. In the board's view, the method of claim 1 finds a basis in the patent application in item 14 referring to item 12, in turn referring to the animal protein-free of item 1.

These items correspond to claims 14, 12 and 1 of the parent application. It is correct that claim 14 of the parent application referred only to claim 1. However, since claim 14 further defines the cell/target protein combination which is for the first time mentioned in independent claim 12, claim 14 makes only technical

sense when read as referring to the method according to claim 12.

12.1 Furthermore, according to paragraph [0047], the method of the invention comprises a) "providing a culture of cells that have been grown in an animal-protein free cell culture medium **according to the invention**, ..." (emphasis added), while the combination of CHO cells/Factor VIII is mentioned in paragraph [0051] and in item 14 as one of three most preferred embodiments, and in examples 2, 5 to 9 and 12 of the patent application.

12.2 The patent application explicitly discloses also an animal protein-free cell culture medium to be used in the method of the invention, as mentioned in item 4 of the patent application, except that the upper limit of the soy hydrolysate concentration is set to 1%. The list of more and more preferred concentration ranges of, the plant- and/or yeast-derived protein hydrolysate in the animal protein-free culture medium explicitly discloses the range from about 0.05% to about 1% (w/v) (see paragraph [0032] of the patent application). The combination of the medium of item 4, defined as comprising a soy hydrolysate, with one of the concentration ranges explicitly disclosed in paragraph [0032] as a preferred embodiment, amounts to a single selection from one single list of concentration.

12.3 Thus, the board considers that the method of claim 1 does not contravene Articles 123(2) EPC and 76 EPC.

Article 56 EPC

13. It was common ground between the parties that document D3 represents the closest prior art for the subject-

matter of claim 1. In the alternative, document D33 represents the closest prior art for the respondent.

13.1 Document D3 relates to an animal protein-free cell culture DMEM/HAM's F12 medium comprising soy extract, preferably between 1 to 5 g/L corresponding to 0.1% (w/v) to 0.5% (w/v) (see page 8, lines 8 to 22). Ultrafiltered soy peptone with an average molecular weight of 350 daltons and a total nitrogen content of approximately 9.5% and a free amino acid content of approximately 13% is advantageously added to said medium. Example 8 describes the culture of recombinant FVIII producing CHO cells in a protein-free and serum-free medium containing different protein hydrolysates, in particular soy hydrolysate at 0.25% (w/v) (see page 22, lines 7-11).

13.2 Document D33 discloses two insect cell media, SF-1 and IP301. The SF-1 medium is stated to have several major advantages over the IP301 medium. However, the animal protein-free cell culture medium "IP301" contains a protein hydrolysate ("Yeastolate") in a concentration of 0.4% (w/v), 1 mg/L spermidine, 1 mg/L spermine.4HCl (corresponding to 0.581 mg/L spermine) and 1 mg/L putrescine.2HCl (corresponding to 0.547 mg/L putrescine).

13.3 The method of claim 1 aims at expressing coagulation factor VIII in CHO cells comprising growing a culture of cells in an animal protein-free cell culture medium, wherein putrescine is present in the culture medium in a concentration ranging from 0.5 to 10 mg/L and soy hydrolysate in a concentration ranging from 0.05 % (w/v) to 1 % (w/v). Since document D3 describes a culture of recombinant FVIII producing CHO cells in a protein-free and serum-free medium, whereas document D33 is

concerned with the production of recombinant proteins in insect cells, the board considers document D3 to represent the closest state of the art.

13.4 The respondent argued that the product characteristics of the soy peptone of document D3 were identical to those of HyPep 1510 as described in document D15, and added preferably at 2.5 g/L (corresponding to 0.25% (w/v)) to the medium (see page 18, Table 2, page 22, lines 8 to 11).

13.5 The board is not convinced by this argument.

13.5.1 First, there is no explicit reference to "HyPep 1510" soy hydrolysate in document D3. Secondly, the ultrafiltered soy hydrolysate having an average molecular weight of 350 Da and a free amino acid content of approximately 13% disclosed in document D3 differs from the soy hydrolysate "HyPep 1510" comprising 7.3% free amino acids according to document D15 or 12% free amino acids when compared to the content of the overall amino acids in the medium. In addition, even if 57% of oligopeptides in the "HyPep 1510" soy hydrolysate have a molecular weight ranging from 200 to 500 Da - irrespective of the fact that there is no information about the distribution of the oligopeptides having this molecular weight - as stipulated in document D15, 43% of them have a different molecular weight. Thirdly, document D3 describes a soy hydrolysate comprising 9.5 % of total nitrogen that is different from the 9.0 % of total nitrogen determined for the "HyPep 1510" soy hydrolysate (see document D15) given the expressed and explicit accuracy of the values. From all these data, the board concludes that the soy hydrolysate used in document D3 is not identical to the "HyPep 1510" from

Quest and therefore cannot be considered to inherently contain 1.48 mg/L putrescine, as determined in Figure 2 of the patent.

13.5.2 Example 8 of document D3 describes the culture of recombinant FVIII producing CHO cells in a protein-free and serum-free medium containing different hydrolysates in particular, as referred to in example 4, a soy hydrolysate at 0.25% (w/v). The soy hydrolysate results in a higher final cell density and an almost twofold higher factor VIII titer than when yeast hydrolysate is used (see page 22, lines 7 to 11, Table 5). Document D3 does nowhere refer to a CHO cell productivity of Factor VIII (Q_p) or a lot-to-lot variability of the soy hydrolysate.

13.6 The difference between the method described in document D3 and the method of claim 1 lies in the use of an animal protein-free cell culture medium comprising putrescine and soy hydrolysate, wherein the putrescine is present in the culture medium in a concentration ranging from 0.5 to 10 mg/L and the soy hydrolysate is present in a concentration ranging from 0.05 % (w/v) to 1% (w/v).

13.7 The effect underlying these differences is that the method enables cells to be cultured so as to achieve an increased cell specific productivity Q_p and a more consistent productivity (i.e. reduced lot-to-lot variability).

13.8 The respondent argued that the patent showed no synergistic effect going beyond the sum of their individual effects and referred to decision T 0605/14 of 7 June 2018). Furthermore, given the scope of claim 1 and the lack of experiments in the patent, there was

no evidence that the technical problem of providing an improved method of expressing a protein using an animal protein-free medium was actually achieved. The experimental results of the patent in Figures 3B and 4B demonstrated, at best, a boosting effect of putrescine on the volumetric productivity.

13.9 Even if the patent discloses that the "HyPep1510" soy hydrolysate at a concentration of 0.4% (w/v) inherently had a putrescine concentration of 2.24 mg/L and that the factor VIII productivity (U/L/D) was increased when CHO cells were cultured in a medium comprising soy hydrolysate from 0.15% to 0.75%, while it decreased again at a concentration of 1%, the board considers that in the absence of any results showing that the use of soy peptones beyond the tested concentrations generates an equivalent cell specific productivity, no conclusion can be drawn in this respect.

13.9.1 Figure 3 compares the volumetric FVIII-CoA productivity of GD8/6 cells as a function of the media used for culture which were supplemented with 5 different lots of soy hydrolysates (0.25 % (w/v) of K119-1, K138-1, M022963, M024423, and M022453) (A) in the absence of putrescine and (B) in the presence of 1 mg/L putrescine.2HCl. The protein productivity was observed to be more consistent and at a higher level.

13.9.2 Figure 4 shows that the specific growth rate of GD8/6 cells ranges at a higher level and is more constant (μ expressed in [d^{-1}] = 1 per day) in media supplemented with different soy hydrolysate lots at a concentration of 0.25 % (w/v) (A) in the absence of putrescine and (B) in the presence of 1 mg/L putrescine.2HCl. Figure 5 summarizes this view.

13.9.3 Figure 9 compares the cell specific productivity (Qp absolute, Qp relative) of GD8/6 cells cultivated in BAV-medium without soy hydrolysate and amines in row 2, with BAV-medium containing a reduced soy hydrolysate concentration of 0.25% (w/v) supplemented with putrescine at the concentration of 3.37 mg/L and 11.25 mg/L. All the media comprising putrescine in Figure 9, except those of rows 2 and 5, are media as defined in the method of claim 1.

13.10 The board considers that, based on the experimental data of the patent, the method for expressing factor VIII in CHO cells in culture media as defined in claim 1 leads to an increased cell specific productivity when compared to the control medium of row 2 as well as to a reduced lot-to-lot variation as shown in Figures 3 and 4. In addition, Figure 5 of the patent shows that the volumetric and cell specific FVIII-productivity and the specific growth rate are considerably increased while the standard deviation observed and calculated from five different lots of soy hydrolysates is significantly reduced in cell culture medium containing 0.25% (w/v) soy hydrolysate plus 1 mg/L putrescine.2HCl, comprising 2.0 mg/L of putrescine (0.08 mg/L + 0.547 mg/L + 1.4 mg/L = 2.0 mg/L), compared to the specific growth rates measured for cells cultured in 0.4% soy hydrolysate comprising approx. 2.24 mg/L putrescine (compare column 3 and 1 of the patent).

13.11 The board considers that in view of the experimental data provided in the patent, the method of claim 1 is capable of both, increasing cell growth, the cell specific productivity and the final cell density, and reducing the effect of the lot-to-lot variability of the soy hydrolysate on the recombinant protein yield.

13.12 Thus, the technical problem to be solved may be defined as the provision of an improved method for expressing factor VIII in CHO cells.

13.13 The solution is the method of claim 1.

Obviousness

13.14 It remains to be established whether the claimed subject-matter was obvious or not to a person skilled in the art at the relevant date.

13.15 The board shares appellant I's view that document D11 refers to the growth and to the cell proliferation effects in the presence of intracellular polyamines. Documents D13 and D18 relate to a serum-free medium comprising insulin and/or transferrin. They do not qualify as an animal protein-free medium according to the invention. Document D18 in example 2 second paragraph relates only to the use of a hypothetical culture medium formulation (see present tense). Document D25 relates to the use of yeast hydrolysate for the production of human thrombopoietin and not to soy hydrolysate for the production of Factor VIII. There is no reference to CHO cells and to an improved recombinant Factor VIII production and/or productivity and of a reduction of lot-to-lot variability allowing for a more constant production of the recombinant protein, in any of these documents. Thus there is no motivation for the skilled person, faced with the technical problem identified above, to combine document D3 with document D5 based on any of these documents.

13.16 Document D5 describes a biochemically defined culture medium for culturing engineered Chinese hamster ovary

(CHO) cell lines, which is essentially free from protein, lipid and carbohydrate isolated from an animal source because the use of serum is problematic.
It was proposed to improve CHO cell growth by adding putrescine at a concentration of 0.5-1 mg/L and by adding hydrolysates at a concentration of 0.25% (w/v).

13.16.1 The board does not share the respondent's view that the skilled person faced with the technical problem defined above would have combined the teaching of documents D3 and D5, as document D5 discloses only media in its examples with recombinant insulin and putrescine.2HCl at a concentration of 0.16 mg/L (i.e. approximately 0.088 mg/L putrescine) which are not those defined in the method of claim 1.

13.16.2 The skilled person starting from the method described in document D3, faced with the technical problem of providing an improved method for producing Factor VIII in CHO cells with a reduced variability, had no motivation to selectively modify the concentration of putrescine to range from 0.5 mg/L to 10 mg/L while keeping all the remaining ingredients the same.

Even if, for the sake of the argument, the skilled person would have combined documents D3 and D5, the board is not convinced that the skilled person had any reasonable expectation of successfully improving the Factor VIII productivity in CHO cells, beyond mere cell growth, let alone combined with a reduction of the variability of Factor VIII productivity attributed to the lot-to-lot variation of soy hydrolysates.

13.17 Thus, starting from document D3, the skilled person without a pointer would not have arrived at the claimed solution in an obvious way. Hence, the solution of

claim 1 involves an inventive step. The considerations for claim 1 apply to dependent claim 2.

14. Hence, the board concludes that auxiliary request 3 fulfills the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in accordance with claims 1 to 2 of new auxiliary request 3, filed as "auxiliary request 9 (corrected)", under cover of a letter dated 15 June 2020, and a description to be adapted.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated