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Datasheet for the decision of 12 January 2024

Case Number: T 0819/21 - 3.3.08

Application Number: 13720203.2

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Title of invention:
Cell culture compositions and methods for polypeptide production

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponents:
Breuer, Markus
Grünecker Patent- und Rechtsanwälte
PartG mbB

Headword:
Cell culture compositions/HOFFMANN-LA ROCHE

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Amendments in all requests - allowable (no)

Decisions cited:
G 0011/91, G 0002/10, G 0003/89

Catchword:
-

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Case Number: T 0819/21 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 12 January 2024

Appellant: (Opponent 1)	Breuer, Markus Brienner Straße 1 80333 München (DE)
Representative:	Breuer, Markus Sendlinger Straße 29 80331 München (DE)
Respondent: (Patent Proprietor)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Party as of right: (Opponent 2)	Grünecker Patent- und Rechtsanwälte PartG mbB Leopoldstrasse 4 80802 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 March 2021 concerning maintenance of the European Patent No. 2841561 in amended form**

Composition of the Board:

Chair	T. Sommerfeld
Members:	B. Claes
	R. Winkelhofer

Summary of Facts and Submissions

I. The appeal lodged by opponent 1 (appellant) lies from the opposition division's interlocutory decision that European patent No. 2 841 561, with the set of claims of the main request, and the invention to which it relates met the requirements of the EPC. The patent with the title "*Cell culture compositions and methods for polypeptide production*" was granted for European patent application No. 13720203.2, which had been filed as an international application under the PCT and published as WO 2013/163294 (referred to herein as "application as filed").

Claim 1 of the main request reads as follows:

"1. A method of producing a polypeptide comprising the step of culturing in a cell culture medium a cell comprising an isolated nucleic acid encoding the polypeptide, wherein:

a) the cell culture medium comprises:
from about 200 mg/L to about 1200 mg/L cystine;
from about 0.05 mg/L to about 1.0 mg/L vitamin B2;
from about 0.05 mg/L to about 10.0 mg/L vitamin B6;
from about 0.05 mg/L to about 12.0 mg/L vitamin B9;
from about 0.05 mg/L to about 2.5 mg/L vitamin B12; and
ferric citrate or ferrous sulfate at a concentration of from about 2 µM to about 80 µM;

b) the cell expresses the polypeptide; and

c) the polypeptide is isolated from the cell culture medium, wherein the isolated polypeptide is concentrated to provide a composition comprising a polypeptide at a concentration of at least 100 mg/ml and wherein the composition has a color reference standard value selected from any one of B4-B9, BY4-BY7, Y4-Y7, GY4-GY7 and R4-R7 according to the European Pharmacopoeia color standards, European Pharmacopoeia, 2008, 7th Edition, Page 22."

II. With the statement of grounds of appeal the appellant filed arguments that, contrary to the opposition division's decision, claim 1 of the main request related to added subject-matter (Article 123(2) EPC).

III. In the reply to the appeal, the patent proprietor (respondent) argued that the opposition division had rightly concluded that claim 1 of the main request complied with the requirements of Article 123(2) EPC, and re-submitted sets of claims of the main request and auxiliary requests 1 to 6 as filed with the submission of 9 December 2020 before the opposition division.

As compared with claim 1 of the main request (see section I.), in claim 1 of auxiliary request 1 the preamble has been amended to provide that the cell to be cultured is a mammalian cell: "comprising the step of culturing in a cell culture medium a mammalian cell comprising an isolated nucleic acid encoding the polypeptide" (amendment underlined).

As compared with claim 1 of the main request, in claim 1 of auxiliary request 2 the preamble has been amended

to provide that claimed is a method "comprising the step of culturing in a cell culture medium a Chinese hamster ovary (CHO) cell comprising an isolated nucleic acid encoding the polypeptide" (amendment underlined).

As compared with claim 1 of the main request, in claim 1 of auxiliary request 3 each instance of the wording "polypeptide" has been replaced with the wording "antibody".

As compared with claim 1 of the main request, in claim 1 of auxiliary request 4 the preamble has been amended to provide that claimed is a "method of producing a polypeptide drug product comprising the step of culturing in a cell culture medium a cell comprising an isolated nucleic acid encoding the polypeptide" (amendment underlined).

As compared with claim 1 of the main request, in claim 1 of auxiliary request 5 the preamble has been amended to provide that claimed is a "method of producing a composition comprising a polypeptide drug product and a pharmaceutically acceptable carrier, the method comprising the step of culturing in a cell culture medium a cell comprising an isolated nucleic acid encoding the polypeptide" (amendment underlined). In addition, the wording "and wherein the polypeptide is combined with the pharmaceutically acceptable carrier" has been added to the end of the claim.

As compared with claim 1 of the main request, in claim 1 of auxiliary request 6 part c) has been amended to read "a composition comprising a polypeptide at a concentration of at least 100 mg/ml or 125 mg/mL or 150 mg/mL, or at a concentration of 100 mg/mL or

125 mg/mL or 150 mg/mL or 175 mg/mL or 200 mg/mL"
(amendment underlined).

IV. The parties were summoned to oral proceedings and the board subsequently issued a communication pursuant to Article 15(1) RPBA providing the board's preliminary appreciation of substantive and legal matters concerning the appeal. The board *inter alia* expressed the opinion that claim 1 of the main request and of all the auxiliary requests did not comply with the requirements of Article 123(2) EPC.

V. Apart from a letter announcing that they would not be represented at oral proceedings, no submissions were made in appeal by opponent 2.

VI. The parties' submissions and arguments on appeal are taken into consideration in the reasons for the decision below.

VII. The appellant requests that the decision under appeal be set aside and amended such that the patent be revoked.

The respondent requests that the appeal be dismissed (main request) or that the patent be maintained on the basis of auxiliary requests 1 to 6 filed with the reply to the appeal.

Reasons for the Decision

Added subject-matter (Article 123(2) EPC)

1. The claims of the application as filed that are relevant to this decision are claims 19, 23 to 25, 27 and 40 to 42. The parts of the description of the application as filed that are relevant to this decision are paragraphs [0007], [0021], [0077], [0145], [0146], [0147], [0161] and [0168].

Main request - claim 1

2. The so-called "gold standard" for assessing compliance with Article 123(2) EPC is that any amendment to the parts of a European patent application as filed or a European patent relating to the disclosure is subject to the mandatory prohibition on extension laid down in Article 123(2) EPC. Therefore, irrespective of the context, an amendment 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 whole of these documents as filed. After the amendment, the skilled person must not be presented with new technical information (see decisions G 3/89, OJ EPO 1993, 117; G 11/91, OJ EPO 1993, 125 and G 2/10, OJ EPO 2012, 376 and "Case Law of the Boards of Appeal of the EPO", 10th edition 2022, "CLBA", II.E.1.1).

3. The opposition division held that the claim had a basis in the application as filed, and thus complied with the requirements of Article 123(2) EPC, when starting from

claims 19, 24 and 25 as filed combined with the preferred colour scheme in Table 2 and the disclosures in paragraphs [0002] and [0003], [0077], [0161] and [0168]. On appeal, in defence the respondent submitted an alternative approach for arguing that the claims complied with the requirements of Article 123(2) EPC. In the following, both the opposition division's approach as well as the respondent's alternative approach are assessed.

Assessment starting from claim 19 as filed

4. The board agrees with the appellant, and thus disagrees with the opposition division, that when starting from claim 19 as filed, deriving the claimed subject-matter requires the selection of various features from a number of lists of alternatives.

5. Claim 19 of the application as filed reads as follows:

"19. A method of producing a polypeptide comprising the step of culturing in a cell culture medium a cell comprising an isolated nucleic acid encoding the polypeptide, wherein:
(a) the cell culture medium comprises:
from about 200 mg/L to about 1200 mg/L cystine;
from about 0.05 mg/L to about 1.0 mg/L vitamin B2;
from about 0.05 mg/L to about 10.0 mg/L vitamin B6;
from about 0.05 mg/L to about 12.0 mg/L vitamin B9;
from about 0.05 mg/L to about 2.5 mg/L vitamin B12; and
(b) the cell expresses the polypeptide".

6. Combining claim 19 with claims 23 and 24, i.e. providing that the cell culture medium comprises ferric citrate or ferrous sulfate as the iron source, already involves a selection of the particular medium in

claim 19 with an iron source (claim 23) over a medium with hydrocortisone alone instead of the iron source (see claim 27 with reference to claim 19), or both hydrocortisone and an iron source (see claim 27 with reference to claim 23). The selection from the medium type based on the claims as filed therefore amounts to a first selection from a list containing three alternatives.

7. The board further notes in this context that claim 25 as filed specifies the cell culture medium in claim 19 as further comprising ferric citrate in a concentration of "from about 2 µM to about 80 µM", but fails to specify this concentration for ferrous sulfate as referred to in the claim.

8. In order to arrive at the claimed subject-matter, the above-selected medium type disclosed in the claims as filed needs further combination with the feature in the claim defining the concentration of the polypeptide present in the composition, i.e. "at least 100 mg/ml", from a list of concentrations disclosed in paragraphs [0145] and [0161] ranging from at least 1 mg/ml, 25 mg/ml, 50 mg/ml, 75 mg/ml, 100 mg/ml, 125 mg/ml to 150 mg/ml. The opposition division's position in this context that "*100 mg/ml is an end point which is singled out*" therefore must fail. The selection of the concentration of the polypeptide present in the composition of "at least 100 mg/ml" for combination with the medium disclosed in claim 19 as filed therefore amounts to a further selection from a list of a considerable number of alternative concentrations.

9. In addition, the respondent's further argument in this context that the disclosure in paragraph [0168] singled out the desired concentration of "at least 100 mg/ml"

as the concentration of the produced polypeptide must also fail because the paragraph, contrary to the claim under consideration, does so solely with reference to production of monoclonal antibodies for intravenous delivery, features which are absent from the claim. Therefore, this paragraph cannot be considered relevant to the disclosure of the claimed subject-matter and relying on it for disclosure may at most amount to a non-allowable intermediate generalisation.

10. Moreover, in order to arrive at the claimed subject-matter, the combinations referred to above have yet to be further combined with a selection of the particular method for assessing the colour of the composition using a particular visual colour standard referred to in the claim, i.e. the particular colour reference standard values "according to the European Pharmacopoeia color standards, European Pharmacopoeia, 2008, 7th edition, page 22". Indeed, the application as filed discloses both visual (see paragraphs [0146] and [0161]) and quantitative (see paragraph [0147]) methods, and for the former two particular alternatives for assessing the colour, i.e. the "United States Pharmacopoeia color standard" and the "European Pharmacopoeia color standard". The selection of the European colour standard therefore amounts to yet another selection from a list of alternatives, which, contrary to the opposition division's opinion, does constitute a selection from a list of three technical alternatives in this case.

11. Additionally, the board agrees with the appellant that the claims as filed do not define a solution with a protein concentration of at "least 100 mg/ml" *in combination* with the particular ranges of colour nuances defined in the claim, i.e. one of B4-B9, BY4-

BY7, Y4-Y7, GY4-GY7 and R4-R7, as in the European Pharmacopoeia colour standard, as defined in the claim. The same holds true for the various disclosures of these particular ranges of colour nuances in paragraphs [0146] and [0161], which are in fact disclosed in these paragraphs each time in combination with various concentrations of protein including but not limited to "at least 100 mg/ml" (see point 9. above). The specific medium of the claim is also not disclosed in the application as filed with the particular ranges of colour nuances referred to in the claim. The fact that Table 2 of the application as filed designates these colour nuances as "most preferabl[e]" does not change this finding.

12. In view of the above considerations it cannot be concluded from the approach starting from claim 19 as filed, which is adhered to by the opposition division, that the claimed subject-matter is directly and unambiguously derivable by the skilled person from the application as filed.

Assessment adhered to by the respondent on appeal

13. This approach starts from the core technical teaching of the application as filed as allegedly summarised in paragraphs [0007] and [0168], i.e. the problematic increase in colour intensity that can occur when polypeptides are formulated at concentrations of 100 mg/mL or greater, and from the solution to this problem by modifying the cell culture medium used to produce the polypeptide. In particular, in the respondent's opinion, paragraph [0168] provided an explicit pointer to work with polypeptides at a concentration of at least 100 mg/mL and these disclosures guided the skilled person to passages

elsewhere in the application as filed that provide the claim wording.

14. However, first, paragraph [0007] makes reference to two concentrations for protein-based drug products with an acceptable colour while maintaining a desired protein-based drug product concentration, namely ≥ 100 mg/mL and ≥ 150 mg/mL. Furthermore and second, the board cannot concur with the respondent that the disclosure in paragraph [0168] singles out the desired concentration of "at least 100 mg/ml" as the concentration of the produced polypeptide in a general sense, because this paragraph, contrary to the claimed subject-matter, refers to this concentration solely with reference to the production of monoclonal antibodies for intravenous delivery, a feature which is absent from the claim (see point 8. above). Contrary to the respondent's submission, the presence of an explicit pointer to work with polypeptides at a concentration of at least 100 mg/mL therefore cannot be acknowledged in this context.

15. The respondent then further argued that, from the "*core*" technical teaching of the application as summarised in paragraphs [0007] and [0168], the skilled person would also turn to paragraph [0021], which allegedly teaches that polypeptides can be isolated and concentrated to achieve a desirable concentration and refers to a composition comprising the isolated polypeptide at a concentration of at least 100 mg/mL. A similar disclosure was found in paragraph [0145].

16. However, in paragraph [0021], a concentration of at least 100 mg/mL can only be considered to be disclosed in a list of possible concentrations ranging from at least 1 mg/mL to 150 mg/mL. A similar list of

concentrations is equally disclosed in paragraph [0145] (see also point 8. above). Therefore, the feature "at least 100 mg/ml" in those paragraphs evidently needs to be selected from a list of alternatives without a pointer guiding the skilled person to it.

17. The respondent has further referred to claim 42 as constituting a pointer to the concentration feature for the polypeptide "at least 100 mg/mL"; however, and with reference to claims 40 and 41, this particular concentration is not disclosed in the context of the same culture medium as referred to in the claim (see points 6., 7. and 20.). Claim 42 as filed therefore cannot be acknowledged as a pointer either.

18. The respondent lastly argued that, when starting from the core technical teaching of the application, for the colour feature the skilled person would turn to paragraph [0161], which teaches that compositions are provided "*comprising a polypeptide at a concentration of at least 100 mg/ml [...] and wherein the composition has a color reference standard value selected from any one of B4-B9, BY4-BY7, Y4-Y7, GY4-GY7 and R4-R7*"; however, neither paragraph [0161] nor paragraph [0146] in fact discloses the particular ranges of colour nuances defined in the claim in direct combination with the concentration "at least 100 mg/ml" (see point 11. above), but actually instead in combination with various concentrations of protein. Accordingly, the combination of the feature "at least 100 mg/ml" with the particular ranges of colour nuances defined in the claim also needs to be selected from a list of alternatives. The fact that the colour reference standard values mentioned in the claim are described as being most preferable in Table 2 does not provide the skilled person with a pointer to an explicit disclosure

of the combination of these particular ranges of colour nuances with the feature "at least 100 mg/ml" (see also point 11.).

19. As outlined in point 10. above, it can be concluded on a more general level that the application as filed discloses both visual (see paragraphs [0146] and [0161]) and quantitative (see paragraph [0147]) methods. In addition, both paragraphs [0146] and [0161] disclose two particular alternatives for the visual colour standard used for assessing the colour, i.e. the "United States Pharmacopoeia color standard" and the "European Pharmacopoeia color standard". Therefore, selecting the European color standard nuances as referred to in paragraphs [0146] and [0161] requires a selection from a list of disclosed alternatives.

20. For the specific culture medium recited in the claim, in the context of the alternative approach, the respondent referred to the medium disclosed in the second sentence of paragraph [0077]. Since the invention was concerned with making modifications to the cell culture media that alleviated the problem of colour intensity when polypeptides were formulated at 100 mg/mL, the fact that the medium was singled out in the paragraph, as well as the pointers in the claims and the examples of the application, taught the skilled person that this medium was particularly suitable in this respect. In particular, claims 19, 23 and 24 as filed provided the clear pointer to the selection of the medium containing the components claimed.

21. However, with reference to point 6. above, combining claim 19 with claims 23 and 24 involves the selection from the medium type based on the claims as filed from a list containing three alternatives. These claims

therefore cannot be acknowledged as providing a pointer to the claimed invention (see also point 7. above).

22. As far as the examples of the application as filed are concerned, these also disclose various media, meaning that the culture medium in the claim would at best be understood to be one embodiment among alternatives for use in the claimed methods. Furthermore, the examples as filed also fail to disclose a link between the medium in the claim and the colour limitations in the claim.

23. Therefore, with regard to the above considerations, paragraph [0077] merely discloses a list of at least five distinct cell culture media, including that in the claim, without any pointer to them or qualifying any of them as being more or less preferred. Accordingly, at most, the paragraph lists equivalently suitable alternative media for application in the invention. The selection of the very medium referred to in the claim from the disclosure in paragraph [0077] therefore can only amount to a further arbitrary selection from a list of alternatives. There is also no link between any of the listed media and the colour limitations in the claim.

Conclusion

24. In view of the above considerations the claimed subject-matter does not meet the requirements of Article 123(2) EPC.

Auxiliary requests 1 to 6 - claim 1

25. As was already expressed in the board's communication pursuant to Article 15(1) RPBA (see section IV.), none

of the amendments in claim 1 of any of these auxiliary requests (see section III.) is of such a nature as to overcome the objections under Article 123(2) EPC raised for claim 1 of the main request. The respondent has not provided any arguments to the contrary.

26. Claim 1 of the auxiliary requests thus likewise fails to meet the requirements of Article 123(2) 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 Chair:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated