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**Datasheet for the decision
of 3 July 2012**

Case Number: T 0990/09 - 3.3.08
Application Number: 00969319.3
Publication Number: 1220893
IPC: C12N 5/00, C12N 5/06
Language of the proceedings: EN

Title of invention:

Medium for the protein-free and serum-free cultivation of cells

Patentee:

Baxter Aktiengesellschaft

Opponents:

Merck Serono SA
Maxygen Inc.
Sigma-Aldrich Co.
Kerry Ingredients (UK) Limited
Novo Nordisk A/S
F.Hoffmann-La Roche AG
Novartis AG
Campina Nederland Holding B.V.

Headword:

Cell culture medium/BAXTER

Relevant legal provisions:

EPC Art. 54, 123(2), 111(1)
RPBA Art. 13(1)

Keyword:

"Admission of the main request and auxiliary request I filed at the oral proceedings (yes)"

"Auxiliary request I: added matter (no)"

"Novelty (yes)"

"Remittal (yes)"

Decisions cited:

T 0472/92

Catchword:

-



Case Number: T 0990/09 - 3.3.08

DECISION
of the Technical Board of Appeal 3.3.08
of 3 July 2012

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Decision under appeal: Decision of the Opposition Division of the European Patent Office posted 20 March 2009 revoking European patent No. 1220893 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: T. J. H. Mennessier
C. Heath

Summary of Facts and Submissions

- I. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division dated 20 March 2009, whereby European patent No. 1 220 893, which had been granted on European application No. 00 969 319.3 (published as international application WO 01/23527), was revoked. Basis for the revocation were the main and the first auxiliary requests filed with the letter of 12 January 2009 as well as the first and the second auxiliary requests filed at the oral proceedings held on 27 January 2009.
- II. Reasons for refusal were (i) non-compliance with the requirements of Article 123(2) EPC for the main request and the first auxiliary request of 27 January 2009, (ii) presence of amendments which were not occasioned by a ground of opposition (see Rule 80 EPC) for the first auxiliary request of 12 January 2009, and (iii) lack of novelty for the second auxiliary request of 12 January 2009 (see Article 54 EPC).
- III. The patent had been opposed by eight parties (opponents 01 to 08 which are respondents I to VIII).
- IV. A main and four auxiliary requests (I to IV) were filed on 20 July 2009 together with the statement of grounds. The main request and auxiliary request I were then replaced by two new sets of claims filed with the letter of 30 July 2009. Auxiliary requests II to IV were re-filed with the same letter.
- V. Respondents I, III, V, VI and VII replied to the statement of grounds.

- VI. On 12 July 2010, the appellant filed a new main request and four new auxiliary requests (I to IV) to replace all requests then on file.
- VII. On 8 March 2012, the Board issued a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) expressing its preliminary and non-binding views.
- VIII. Each of respondents I, III, VI and VII replied to the Board's communication.
- IX. The appellant replied to the Board's communication with a letter dated 1 June 2012, to which a main request and nine auxiliary requests were attached. These requests replaced the previous ones. The main request corresponded to the main request of 12 July 2010. The first, second and sixth auxiliary requests corresponded to the first, third and fourth auxiliary requests of 12 July 2010, respectively. The third, fourth, fifth, seventh, eighth and ninth auxiliary requests were new.
- X. Oral proceedings took place as scheduled on 3 July 2012. They were attended by all parties except respondents II, IV and VIII, who announced that they would not be represented in their respective letters of 27 June 2012, 12 June 2012 and 18 June 2012.
- XI. In these oral proceedings the appellant filed a new main request and two new auxiliary requests. All other requests were explicitly withdrawn. At the end of the oral proceedings, the appellant withdrew the first

auxiliary request. The remaining auxiliary request was re-filed as auxiliary request I.

- XII. The main request and auxiliary request I consisted each of one claim.

Main request:

"1. A protein-free and serum-free medium for the cultivation of mammalian cells comprising ultrafiltered soy hydrolysate, wherein at least 40% of said soy hydrolysate has a molecular weight of \leq 500 Dalton."

Auxiliary request I:

"1. A process for the production of recombinant factor VIII from cell culture comprising:
introducing mammalian cells that contain sequences which code for recombinant factor VIII into a protein-free and serum-free medium comprising ultrafiltered soy hydrolysate, wherein at least 40% of said soy hydrolysate has a molecular weight of \leq 500 Dalton;
wherein said cells express recombinant factor VIII;
growing said cells in said medium and expressing said recombinant factor VIII, thereby producing a mixture of said cells and said recombinant factor VIII in said medium;
purifying said recombinant factor VIII from said mixture."

- XIII. The following documents are referred to in the present decision:

(E4) WO 02/24876 (published on 28 March 2002, claiming the priority date of 25 September 2000)

(E45) Quest International product Information retrieved on 21 March 2007 from the internet file
'file:///Documents%20and%20Settings\mmurphy\Local%20Settings\Temporary%20...'

(E68) A set of print-outs from the web-archive retrieved on 1 August 2007 from the internet sites
'http://web.archive.org/web//http://www.sheffield-products.com/pharma_ingredients/...'* (1 page)
'http://web.archive.org/web/20030518162635/http://www.sheffield-products.com/pharm...' (1 page)
'http://web.archive.org/web/20000308080227www.sheffield-products.com/products/5...' (2 pages)
and
'http://web.archive.org/web/20000303141221/www.sheffield-products.com/hydrol.thm' (1 page)

(E79) Declaration of Anthony Kunst dated 27 November 2008

XIV. The submissions made by the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility of the main request and of auxiliary request I

The negative conclusions reached by the Board at an early stage of the oral proceedings with regard to the requirements of Article 123(2) EPC could not have been foreseen in light of the preliminary opinion given in the communication pursuant to Article 15(1) RPBA. The appellant could not have been expected to submit

amendments in this respect in preparation for the oral proceedings. Furthermore, the subject-matter of the two new requests, each consisting of one claim only, was already present in requests filed with the statement of grounds of appeal.

Main request (Article 54 EPC)

The terms '*hy-soy/UF, Quest 5X59100*' and '*hy-pep 1510 Quest*', mentioned at lines 30 and 32 of page 9 in document E4, without the indication of any additional technical features, did not provide clear guidance as to the nature of these products. 'Hy-soy/UF' was not mentioned at all in the present patent. Without any reference to a 'Quest' catalogue number, the 'hy-pep 1510' product referred to in document E4 could not have been unambiguously identified. Document E4 provided a non-enabling disclosure of the SF-medium. It had not been proven 'up to the hilt' that the SF-medium of document E4 was a medium according to claim 1.

The archived web page of document E68 with the address: '<http://web.archive.org/web/20030518162635/http://www.sheffield-products.com/phar...>' (see bottom of the page) which referred to 'HyPep 1510' as a high quality source of ultrafiltered peptides obtained from enzymatic hydrolysis of soy was archived on 18 May 2003, as derivable from its http address, i.e. after the priority date of document E4. A comparison of this archived web page, which contained the term 'Hy-Pep 1510[®] (IPL:5X59053)' (see top of the page), with the product information notice filed as document E45 with a date of 21 March 2007 (see the bottom of the two pages of document E45), which contained the term 'HyPep[®]

1510 (IPL:5Z10493)', showed that 'Quest' had changed its catalogue number between 2003 and 2007. Therefore, there was no guarantee that the product had remained the same over the time.

Auxiliary request I

Article 123(2) EPC

Support for the subject-matter of claim 1 could be found in claim 14, taken in combination with claims 1 and 15, on page 11, last paragraph and page 12, lines 5 to 8, in the application as filed. The omission of the feature - given at page 12, lines 10 to 12 as filed with respect to the recombinant cells - '*that are capable of expressing these in a stable manner over several generations*' was irrelevant. This feature was indeed an implicit one. Furthermore, page 13, second paragraph as filed described the use of the medium in accordance with the invention for the cultivation of recombinant cells, especially, mammalian cells, without mentioning any condition in relation with the stability of the protein expression. Therefore, there was no need to mention this feature in claim 1.

Articles 123(3), 84 and 54 EPC

No objections were raised by the respondents. The requirements of these Articles were met.

Remittal

Should the Board decide that the claims of auxiliary request 1 met the requirements of Articles 123(2),

123(3), 84 and 54 EPC, the case should be remitted to the first instance for further prosecution.

- XV. The submissions made by the respondents, insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility of the main request and of auxiliary request I

The main request and auxiliary request I, both submitted at the oral proceedings, were late filed. As they contained added subject-matter, they were *prima facie* not admissible.

Main request (Article 54 EPC)

The two archived web pages with the address '<http://web.archive.org/web/20000308080227/www.sheffield-products.com/products/5...>' of document E68 showed the date of 8 March 2000, i.e. prior to the priority date of document E4. They unambiguously described 'HyPep 1510' as an ultrafiltered soy hydrolysate with a molecular distribution of weight such that 25,4% + 57,5% = 82,9 % thereof had a molecular weight less than or equal to 500 daltons. There was no indication in the documents on file that the technical features of 'HyPep1510' had changed over the time and the appellant had not provided any convincing evidence in this respect. The appellant had not denied that 'HyPep 1510' was available from 'Quest' at the priority date of document E4.

Auxiliary request I

Article 123(2) EPC

The method of claim 1 was not explicitly described in the application as filed. On page 12, lines 5 to 12 reference was made to cell clones which contained the coding sequence for a recombinant blood factor, such as factor VIII, and were capable of expressing it in a stable manner over several generations. This essential technical feature was not present in claim 1, which therefore did not meet the requirements of Article 123(2) EPC.

Article 123(3), 84 and 54 EPC

No comments were made with respect to the requirements of these Articles.

Moreover, the respondents expressed no objections concerning a possible remittal of the case to the first instance for further prosecution.

XVI. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the case be remitted to the first instance for further prosecution based on the main request, or on auxiliary request I, both filed during oral proceedings.

XVI. The respondents (opponents) requested that the appeal be dismissed.

Reasons for the decision

Admissibility of the main request and of auxiliary request I

1. Each of the two requests represents an amendment to the appellant's case which was made after it had filed its ground of appeal and which, therefore, may be admitted and considered at the Board's discretion (see Article 13(1) RPBA).
2. The main request consists of one claim only, which is identical to claim 1 of the main request that was the basis for the decision under appeal and of each of the main requests filed on 20 July 2009 (submitted with the statement of grounds), 30 July 2009, 12 July 2010 and 1 June 2012.
3. Auxiliary request I also consists of one claim, which is identical to claim 1 of auxiliary request IV of 20 July 2009 (submitted with the statement of grounds), of auxiliary IV of 30 July 2009, and of auxiliary VI of 1 June 2012 only in that the terms "recombinant"
4. Both requests were filed in direct reaction to the negative conclusion reached by the Board at an early stage of the oral proceedings with regard to the then pending requests under Article 123(2) EPC.
5. The Board has given a positive opinion on this issue in its communication of 8 March 2012, and it agrees with the appellant that there was no reason to submit amended requests in preparation for the oral proceedings. In view of this situation and considering the nature of the new requests, which do not add to the

complexity of the case, the Board, exercising its discretion, decides to admit the main request and auxiliary request I into the proceedings.

Main request (Article 54 EPC)

6. Claim 1 is directed to a protein-free and serum-free medium for the cultivation of mammalian cells. The medium comprises an ultrafiltered soy hydrolysate, at least 40% of which has a molecular weight less than or equal to 500 daltons (see Section XII *supra*). As no endotoxin content is specified regarding the soy hydrolysate in claim 1, said technical feature is to be ignored for the novelty assessment.
7. The respondents have argued that such a medium was described in document E4 and that, consequently, claim 1 was not novel. Document E4 which benefits from a priority date (25 September 2000) that is prior to the filing date claimed for the patent at issue (27 September 2000) is cited under the provisions of article 54(3) EPC.
8. The priority document of the patent at issue fails to describe a medium comprising an ultrafiltered soy hydrolysate, at least 40% of which has a molecular weight **less than or equal to 500 daltons**. Indeed, only hydrolysates, at least 40% of which have a molecular weight **from 200 to 500 daltons** are described (see page 5, last paragraph, and claim 5). Moreover, according to the priority document it is an essential feature of the medium that it has an endotoxin content of less than 500 endotoxin-unities per gram. Therefore, claim 1 of the main request is not entitled to its

claimed priority date and the relevant date to be considered for the novelty assessment is the international filing date, i.e. 27 September 2000, which is later than the priority date of the post-published document E4. Consequently, document E4 belongs to the state of the art pursuant to Article 54(3) EPC.

9. The relevant passage of document E4, relied on by the respondents, is Example 1, which describes a medium referred to as the 'SF-medium', used for the cultivation of Vero cells (see document E4, page 9, line 23 to page 10, line 2). This medium consisted of a mixture of DMEM, Ham's F12 and L-Gln which was supplemented with a solution of one of two protein hydrolysates referred to respectively as the 'hy-soy/UF, Quest 5X59100' and the 'hy-pep 1510, Quest' (see page 9, lines 25 to 33). The content of a deep frozen ampoule of Vero cells - which are mammalian cells - was thawed and added to 9 ml of SF-medium. After centrifugation for 10 min at 1000 rpm, the pellet was resuspended in SF-medium, transferred to a Roux bottle and incubated at 37 °C and 7% CO₂ for at least 15 minutes. Therefore, the respondents have argued, that document E4 clearly and unambiguously describes a protein-free and serum-free medium for the cultivation of mammalian cells comprising a protein hydrolysate. For the Board it remains to be assessed whether a skilled person at the priority date of document E4 was in a position to establish that one of the two protein hydrolysates was an ultrafiltered soy hydrolysate, at least 40% of which had a molecular weight less than or equal to 500 daltons.

10. The question to be answered is whether there is sufficient evidence on file to convincingly establish, by applying the balance of probabilities as the standard of proof, that an ultrafiltered soy hydrolysate, at least 40% of which having a molecular weight of less than or equal to 500 daltons, was available to the public at the priority date of document E4 under one of the two designations 'hy-pep 1510' and 'hy-soy/UF'.

11. An answer to this question is provided by the two product information web pages from 'Quest international' of document E68, bearing the address '<http://web.archive.org/web/20000308080227/www.sheffield-products.com/products/5...>' (emphasis added by the Board). As derivable from the address, and as argued by in particular respondent I at the oral proceedings, said web pages were archived on 8 March 2000. This has not been contested by the appellant which at the same oral proceedings has similarly indicated that the another web page of document E68 bearing the address '<http://web.archive.org/web/20030518162635/http://www.sheffield-products.com/phar...>' (emphasis added by the Board) was archived on 18 May 2003.

12. As the two product information web pages mentioned in point 11 above were archived on 8 March 2000 they were made publicly available on the web at a date prior to the priority date of document E4. They describe 'HyPep 1510' as an ultrafiltered soy hydrolysate, 25,4% of which having a molecular weight less than 200 daltons and 57,5% of which having a molecular weight comprised in the closed interval of 200 to 500 daltons.

13. Therefore, it can be concluded that an ultrafiltered soy hydrolysate, at least 40% of which having a molecular weight less than or equal to 500 daltons, has been commercialised by 'Quest international' before the priority date of document E4.

14. The appellant has argued that it was possible that the trademark 'HyPep 1510' had been used by 'Quest International' to designate a protein hydrolysate having different technical features. It has also contended that 'Quest' could have prepared a special protein hydrolysate to serve the only purpose of providing the SF-supplement of document E4. In the absence of any supporting evidence, these arguments are not tenable.

15. Additionally also document E79 was considered to be highly relevant for the novelty assessment. This document is a declaration, dated 27 November 2008, from Anthonie Kunst, the then R & D Director Proteins of Kerry Bio-Sciences, a company which was the successor of 'Quest International' (Quest). According to this declaration, 'HyPep 1510', which is an ultrafiltered soy hydrolysate (see point 8 of E79), has been commercially available from 'Quest' and its successor since 1997 (see point 5 of document E79). Document E79 also states that the 'HyPep 1510' was available in 1999 and earlier in a form wherein 82,9% of it had a molecular weight of less than or equal to 500 daltons (see point 7 of document E79). Whereas document E79 is silent as to the molecular weight distribution of the 'HyPep 1501' available in 2000 - because the declaration was made in response to questions restricted to the 'HyPep 1510' sold prior to September

1999 - (see point 4 of E79), there is no evidence on file that the composition of 'HyPep 1510' produced between September 1999 and the priority date of document E4 (25 September 2000) had changed. While it is true that the catalogue number used along with the commercial designation 'HyPep 1510' has varied over the time ('IPL:5X59053' on the web page archived on 18 May 2003 of document E68 and 'IPL:5Z10493' on the web pages of the same document archived on 8 March 2003), this does not necessarily mean that the product has changed. It could also represent a change in the presentation of the product only. In view of the evidence on file, the Board concludes that document E79 rather confirms that 'HyPep 1510' described in the two product information web pages of document E68 archived on 8 March 2000 (see point 11 above) is the same as the one referred to in document E4.

16. The appellant has argued that in the present case the 'up to the hilt' standard of proof should be applied rather than the standard of the balance of probabilities. The Board disagrees and asserts that **the 'up to the hilt' standard**, which was first developed in decision T 472/92 (OJ EPO 1998, 161), is to be applied **for cases of public prior use** where practically all the evidence in support of an alleged public prior use lay within the power and knowledge of the opponent(s) (see the Case Law, sixth Edition, 2010, Chapter VI.H, Section 4.3.1, page 558).
17. In view of the above remarks, the Board decides that document E4 describes a medium according to claim 1, which consequently lacks novelty. Therefore, the main

request does not comply with the requirements of Article 54(3) EPC.

Auxiliary request I

Article 123(2) EPC

18. Support for the method of claim 1 can be found in claim 14 of the application as filed, which is directed to a process for the production of a protein from cell culture in a protein-free and serum-free medium according to claim 1, taken together with i) claim 15, which is directed to a cell culture composition comprising mammalian cells and a medium in accordance with claim 1, ii) page 11, last paragraph which indicates that a preferred cell culture was derived from a mammalian cell producing a recombinant protein, and iii) page 12, lines 5 to 8 which states that a preferred recombinant protein was factor VIII. In the absence of evidence of the contrary, the Board shares the appellant's opinion that the capability of expressing factor VIII of the recombinant mammalian cells in a stable manner over several generations, as mentioned on page 12, is to be regarded by a skilled person as an implicit feature of the cells used in the process of claim 1. There is no need to explicitly mention this feature in the claim. Therefore, the Board is satisfied that the requirements of Article 123(2) EPC are met.

Article 123(3) EPC

19. Claim 1 of auxiliary request I is directed to a process for the production of recombinant factor VIII (see

Section XII *supra*). While it has no counterpart in the claims as granted, it features a particular embodiment of the process of granted claim 14 to which it adds the following two technical features: i) the mammalian cells are recombinant and ii) the protein is factor VIII. Therefore, the extent of protection conferred by claim 14 as granted has been restricted. The Board concludes that auxiliary request I complies with the requirements of Article 123(3) EPC.

Article 84 EPC and 54 EPC

20. No objections under Articles 84 and 54 EPC have been raised by the respondents. The Board is satisfied that the claim is clear and supported by the description and that none of the cited prior art documents discloses a method according to the only claim of auxiliary request 1. Thus, the requirements of Articles 84 EPC and 54 EPC are Met.

Conclusions

21. Auxiliary request I complies with the requirements of Articles 54, 84, 123(2) and 123(3) EPC. As requested by the appellant, in order to give it the opportunity to have its case examined by two different instances as regards the requirements of the EPC which have not yet been assessed, the case is remitted to the first instance for further prosecution (Article 111(1) EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution based on auxiliary request I filed at the oral proceedings.

The Registrar

The Chairman

A. Wolinski

M. Wieser