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D E C I S I O N
of 16 July 2002

Case Number: T 0455/96 - 3.3.4

Application Number: 87116556.9

Publication Number: 0277289

IPC: A61K 37/14

Language of the proceedings: EN

Title of invention:

Extra pure semi-synthetic blood substitute

Patentee:

Biopure Corporation

Opponents:

- (01) Baxter International Inc.
(02) Enzon, Inc.
(03) Somatogen Inc.
(04) Hemosol, Inc.
(05) Stichting Centraal Laboratorium van de
Bloedtransfusiedienst van het Nederlandse Rode Kruis
(06) Northfield Laboratories, Inc.

Headword:

Blood substitute/BIOPURE CORPORATION

Relevant legal provisions:

EPC Art. 123(2)(3), 84, 83, 56

Keyword:

"Main request: sufficiency of disclosure (yes), inventive step (yes)"

Decisions cited:

T 0054/90, T 0191/90

Catchword:

-



Case Number: T 0455/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 16 July 2002

Appellant:
(Proprietor of the patent)

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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 18 March 1996
revoking European patent No. 0 277 289 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietor against the decision of the opposition division revoking European patent No. 0 277 289 (application No. 87 116 556.9) filed on 10 November 1987 (priority dates: 10 November 1986 and 13 October 1987), which had been opposed by six parties (opponents 01 to 06) on grounds of Articles 100(a), 100(b) and 100(c) EPC. The patent related to an extra pure semi-synthetic blood substitute and had been granted on the basis of 16 claims, of which claim 7 read as follows:

"7. A blood substitute comprising an aqueous solution of crosslinked hemoglobin, said blood substitute being substantially free of cell stroma, non-hemoglobin proteins and pyrogens and having an endotoxin level which upon in vivo administration does not cause complement activation."

II. The following documents are cited in the present decision:

(D9) US-A-4,001,200;

(D11) US-A-4,584,130;

(D29) Feola M. et al., Surgery, Gynecology & Obstetrics, Vol. 166, pages 211 to 222 (1988);

(D34) DetoxiGel® Brochure from Pierce (1984);

(D38) Loos M. et al., Cancer Research, Vol. 32, pages 2292 to 2296 (1972);

- (D47) Pearson F.C. III et al., BioScience,
Vol. 30, No. 7, pages 461 to 464 (1980);

- (D52) Sehgal L.R. et al., J. Surg. Res. Vol.
30, pages 14 to 20 (1981);

- (D101) Lenz G. et al., Infusionsther.
Transfusionsmed., Vol. 21, Suppl. 3,
pages 63 to 67 (1994);

- (D103) Gilbert V.E. et al., article presented at the
American Association of Immunologists on
April 1962, pages 477 to 490 (Fed. Proc.,
Vol. 21, page 17 (1962));

- (D104) Semeraro N. et al. in "Platelets: A
Multidisciplinary Approach" edited by G.
de Gaetano and S. Garattini, Raven
Press, New York, pages 293 to 302
(1978);

- (D105) Burhop K. et al., Immunopathology,
page A1176, Abstract No. 5116;

- (D106) Dabbah R. et al., J. Parental Drug
Association, May/June 1980, pages 212 to
216;

- (D110) Chenoweth D.E., Artificial Organs,
Vol. 8, No. 3, pages 281 to 287 (1984);

- (D112) US-A-4,324,683;

- (D113) US-A-4,409,335;

(D114) US-A-4,401,652;

(D118) Declaration of Dr. Maria Gawryl dated 10 June 2002.

- III. The reasons given for the refusal was that the main request and first to fifth auxiliary requests submitted at the oral proceedings included claims which lacked novelty vis-à-vis the blood substitute disclosed by document (D11). In view of this negative finding, the opposition division did not deal with the issue of inventive step.
- IV. With letter dated 14 March 2002, opponent 05 withdrew the opposition.
- V. On 3 April 2002, the board issued a communication pursuant to Article 11(2) of the rules of procedure of the Boards of Appeal expressing its provisional opinion.
- VI. Oral proceedings were held on 16 July 2002, during which the appellant submitted a new main request in replacement of all preceding claim requests, the sole claim of which read as follows:

"1. A process for preparing a non-toxic blood substitute comprising an aqueous solution of cross-linked hemoglobin, said blood substitute being substantially free of cell stroma, non-hemoglobin proteins and pyrogens and having an endotoxin level which upon in vivo administration does not cause complement activation, the process comprising the steps of:

- (1) separation of red blood cells from a bovine blood fraction and mechanical degradation of the red blood cells to produce a composite of hemoglobin and stroma, including phospholipids, wherein the separation and mechanical degradation are carried out by centrifugation during which the red blood cells impact an inner surface of a collection chamber of the centrifuge to produce a hemoglobin containing solution;
- (2) clarifying the hemoglobin containing solution to produce a hemoglobin solution which is substantially free of cellular debris;
- (3) separation by microporous filtration and ultrafiltration of the hemoglobin, contaminated with at least a portion of the phospholipid;
- (4) purification of the hemoglobin by ion exchange high performance liquid chromatography (HPLC) to separate the hemoglobin from all other proteins residual of the red blood cells, as well as the phospholipid, enzyme and endotoxin contaminants, wherein the HPLC is carried out using a separation medium comprising silica gel with a surface derivatised to have a quaternary amine type surface property and includes elution of the hemoglobin with buffer to set up a gradient or variable composition flow;
- (5) collecting the effluent from step (4) around its hemoglobin peak;
- (6) cross-linking the hemoglobin; and

- (7) partially separating the cross-linked hemoglobin from the non-cross-linked hemoglobin to produce a product having a defined molecular weight distribution of greater than 90% between 68,000 daltons and 500,000 daltons."

VII. The submissions by the appellant, insofar as they are relevant to the sole claim on file, can be summarized as follows:

Article 83 EPC

- Well known tests were readily available before the priority date of the patent in suit to check whether the blood substitute produced by the claimed process exhibited an endotoxin level which upon in vivo administration did not cause complement activation. The complement activation test was well known to the skilled person (see document (D38), under the heading "Materials and Methods", in particular reference 8). Documents (D103) and (D110) showed that the complement activation test was very reliable. Another test for endotoxin was the limulus amebocyte lysate (LAL) assay, which had been approved by the FDA (see page 22, lines 39-40 of the patent in suit).

- The safety of the blood substitute obtained through the claimed process had been evaluated in numerous clinical trials (see document (D118)). Document (D101) showed that this blood substitute was safe. The fact that the product according to document (D29) was not safe was irrelevant, since it had been obtained by a process involving a DetoxiGel® column.

Article 56 EPC

- Since the claimed process was prima facie not obvious, no need arose to compare the product with that obtained through the process of document (D11).

- By combining the teaching of document (D11) with that of documents (D9), (D52) and (D112) to (D114), the skilled person would not have arrived at the claimed process comprising inter alia the very specific steps of HPLC and mechanical lysis. The latter (ie, step (1) of the claim at issue) achieved the advantageous technical effect pointed out on page 11, lines 8 to 10 of the patent in suit (absence of free small cell membrane components).

VIII. The submissions by the respondents, insofar as they are relevant to the sole claim on file, can be summarized as follows:

Article 84 EPC

- The term "microporous filtration" lacked clarity.

Article 83 EPC

- The claimed process was not enabled because it was difficult or impossible for the skilled person to accurately measure the endotoxin levels of the product obtained through the process. There were indeed substantial differences in levels of endotoxin required to activate the complement not only between animal species but also between members of the same species (see eg document (D105): "in

sheep complement does not play a major role in response to complement activation by endotoxin" and document (D104), according to which LPS (lipopolysaccharides, namely bacterial endotoxins) had a different mechanism for complement activation in rabbits compared to humans (cf. last paragraph). Moreover, the LAL assay was unreliable (see documents (D47) and (D106)). Therefore, the experiments carried out with rabbits, dogs and monkeys according to the description of the patent in suit were not predictive of complement activation in humans by the final product obtained through the claimed process.

- The claimed process was not enabled because the technical problem of preparing a non toxic blood substitute based on cross-linked hemoglobin had not been solved even as of 1994, eight years after the priority date of the patent in suit (see document (D101)). Postpublished document (D29) showed indeed that bovine hemoglobin obtained through the claimed process was toxic (see pages 215 and 220). The cross-linking strategy and the chromatographic medium for obtaining a non-toxic blood substitute without undue experimentation was also not disclosed in the patent in suit.

Article 56 EPC

- The problem to be solved lay with the provision of a further (alternative) process for preparing a non-toxic blood substitute comprising an aqueous solution of cross-linked hemoglobin, said blood substitute being substantially free of cell stroma, non-hemoglobin proteins and pyrogens and having an

endotoxin level which upon in vivo administration did not cause complement activation. Compared with the process disclosed by document (D11), the claimed one included a step of mechanical hemolysis instead of osmotic lysis. This was a known alternative (see documents (D9), (D52) and (D112) to (D114)). Moreover, the appellant did not provide any evidence that said step achieved any advantageous technical effect on the product.

- The appellant's argument that mechanical hemolysis releases less phospholipids than osmotic hemolysis was without merit since these contaminants would be removed anyway by the HPLC step.
- The claim included a step of ion exchange high performance liquid chromatography (HPLC) on a separation medium exhibiting quaternary amine type moieties. The HPLC technique in document (D11) also used such strong anionic resin bearing quaternary amine type moieties (see column 13, line 44: "QAE-25/50").
- A very low endotoxin level could be achieved by using DetoxiGel® (see document (34)). Combining the process of document (D11) with that of document (D34) would have led the skilled person directly to the present invention.

IX. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of:

Claims: Claim 1 as submitted as the New Main Request filed at oral proceedings on 16

July 2002.

Description: Amended pages 2, 5-10, 16-18, 23 and 48-50 as filed at oral proceedings on 16 July 2002.

Pages 3, 4, 11-15, 19-22, 24-47 and 51-59 as granted.

Figures: As granted.

The respondents (opponents 01, 04 and 06) requested that the appeal be dismissed.

Reason for the Decision

1. The appeal is admissible.

Article 123(2) EPC

2. A process comprising steps (1) to (7) is disclosed as a unitary process as such in the application as filed. Step (1) can indeed be derived from Section B on pages 10 to 11 of the published ("A") application as filed, in particular on page 11, lines 29 to 34. Steps (2) to (7) find a basis in Sections C to H of the same document. The same identical steps (1) to (7) are disclosed in Example I as filed, under Sections I to H. Therefore, the claimed process is not an arbitrary selection of features from a "reservoir" but can be directly and unambiguously derived from the application as filed. The claim is thus allowable under Article 123(2) EPC.

Article 123(3) EPC

3. The sole claim contains the full text of claim 7 as granted (see Section I supra) which conferred absolute protection for such a blood substitute, however made. Therefore, any process for making it is narrower in scope. That there is no infringement of Article 123(3) EPC as a result of a change of category, from a product as claimed by the patent as granted, to a process of producing the same has been established in decisions eg T 54/90 of 16 June 1993 and T 191/90 of 30 October 1991. Therefore, the board sees no offence against Article 123(3) EPC.

Article 84 EPC

4. The respondents' objection under Article 84 EPC to the clarity of the expression "microporous filtration" is not considered to be justified as the skilled person knows both from the prior art (cf. document (D11), see e.g. column 13, lines 27 to 35, in particular line 30: "Pellicon cassette (Millipore)) and from the description of the patent in suit (cf. page 19, lines 15 to 28, in particular line 21: "Millipore® Pellicon cassette") what is meant thereby.

Article 83 EPC

5. The respondents raise an objection under this Article arguing that the skilled person is not in a position to accurately establish whether the claimed process leads to a blood substitute "having an endotoxin level which upon *in vivo* administration does not cause complement activation" (see the claim at issue).

Although it is true that the measure of the endotoxin levels by means of the complement activation test

performed on animals can vary between animal species and even between members of the same species, it is a fact that performing a complement activation test *per se* poses no problem as there are many ways for carrying it out. Document (D110) discloses an assay for evaluating complement activation termed C3a RIA. It is "reliable" (see page 281, r-h column) to the extent that it is performed on humans (*ibidem*: "Forty-one patients"). Moreover, endotoxin levels can be evaluated by way of the LAL assay referred to on page 9, lines 14 to 16 of the patent in suit. The fact that this test has been approved by the FDA (see page 22, lines 39 to 40 of the patent in suit) pleads in favour of its reliability. The board thus does not find that a case of insufficiency has been made out because both the endotoxin levels and the complement activation can be measured without any burden by applying standard techniques.

6. It is argued by the respondents that the claimed process is not enabled because it does not yield a blood substitute devoid of toxicity as shown by postpublished documents (D29) and (D101) and that undue experimentation is required for obtaining a non-toxic blood substitute, as the cross-linking strategy and the chromatographic medium are not disclosed in the patent in suit.

As for document (D29), the board observes that the product according to this document is obtained by a process involving a DetoxiGel® column (see page 212, l-h column), ie a process different from the claimed one. Therefore, this product, be it safe or not, is irrelevant for the purpose of the present decision.

As regards document (D101), there is indeed a passage on page 66, l-h column, lines 24ff, according to which

circulatory problems arose upon administration of a bovine "poly-Hb" solution of Biopure (ie the appellant). However, this statement has to be balanced with that at lines 8ff (ibidem), according to which a bovine "poly-Hb" solution made by Feola (one of the inventors of the patent in suit) gave no side effects when administered to children suffering from sickle cell anemia.

7. In conclusion, no evidence is before the board that the claimed process yields a blood substitute which is toxic. Neither can the board share the respondents' contention that the cross-linking strategy and the chromatographic medium are insufficiently disclosed in the patent in suit. This is because no less than four pages (Sections F and G on pages 12 to 16) of detailed information are devoted to these aspects, not to speak of Sections F and G of Example I.

In view of the above findings, the board concludes that no case has been made out that the claim does not satisfy the requirements of Article 83 EPC.

Article 56 EPC

8. The decision under appeal does not deal with the issue of inventive step (see Section III supra). In the present case, there undoubtedly exists a requirement for a speedy procedure since the patent in suit enjoys priority rights from as early as 1986. Since the parties, including the appellant (see point 4.1 of the submission dated 13 June 2002) agree, the Board exercises its discretion under Article 111(1) EPC to decide also this issue.
9. It is argued by the respondents that the effects and advantages of using the claimed process are missing.

Regardless of whether a product is novel and/or inventive, a process therefor can nevertheless involve an inventive step if it does not merely consist of features which are already necessarily and readily derivable in an obvious manner having regard to the state of the art. Therefore, the ultimate and decisive question is whether or not there was a pointer in the prior art which would have directed the skilled person to the claimed process.

10. The claimed method differs from the blood treatment method described in document (D11) **inter alia** by the manner in which the red blood cells are disrupted (step (1) of the claim at issue), which is a mechanical one, more precisely the degradation of the erythrocytes occurs by centrifugation during which the red blood cells impact an inner surface of a collection chamber of the centrifuge to produce a hemoglobin containing solution. The process according to document (D11) makes use of a hypertonic solution to hemolyse the erythrocytes (column 13, lines 25 to 26). Thus, the proper question to be addressed is whether the skilled person was motivated to modify the process disclosed in document (D11) and go into the direction of introducing mechanical lysis by means of a high speed spinning centrifuge, in order to solve the problem of providing an alternative process to that of document (D11).

11. It can be accepted that the skilled person might have taken some methods of mechanical lysis into consideration, eg those disclosed in document (D9) (see column 2, line 59: shaking after addition of cold water), document (D52) (see page 15, paragraph bridging l-h and r-h column: disruption by passage under high pressure through a needle valve), document (D112) (see column 7, line 53: shaking) and document (D114) (see column 2,

line 51: sonication). However, none of these documents would have led the skilled person to the specific mechanical lysis method involving the degradation of the erythrocytes by centrifugation during which the red blood cells impact an inner surface of a collection chamber of the centrifuge to produce a hemoglobin containing solution. The more so, as document (D114), while pointing at "lysing" as a rapid and efficient disruption method, explicitly taught away from "high speed centrifugation" (see column 1, lines 52 to 54).

12. Therefore, the subject-matter of the sole claim at issue cannot be derived in an obvious manner from the prior art.

Order

For these reasons it is decided:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent as requested by the appellant.

The Registrar:

The Chairman:

P. Cremona

L. Galligani