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D E C I S I O N
of 11 December 2002

Case Number: T 0148/98 - 3.3.4

Application Number: 88904862.5

Publication Number: 0358708

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Title of invention:
Blood substitutes

Patentee:
Baxter Biotech Technology S.à.r.l., et al

Opponent:
Apex Bioscience, Inc.

Headword:
BLOOD SUBSTITUTES/Baxter Biotech Technology S.à.r.l., et al

Relevant legal provisions:
EPC Art. 83

Keyword:
"Sufficiency of disclosure - (no)"

Decisions cited:
T 0456/91, T 0923/92, T 0296/93, T 0207/94, T 0595/90

Catchword:
-

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Case Number: T 0148/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 11 December 2002

Appellant I: (Proprietor of the patent)
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Decision under appeal: Interlocutory decision of the Opposition Division of the European Patent Office posted 27 October 1997 concerning maintenance of European patent No. 0 358 708 in amended form.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: M. R. J. Wieser
S. U. Hoffmann

Summary of Facts and Submissions

I. The appellants I (patent proprietors) and appellants II (opponents) lodged appeals against the interlocutory decision of the opposition division on the amended form in which European Patent No. 0 258 708 can be maintained.

Opposition was filed against the grant of the patent as a whole under Article 100(a) on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) on the ground of lack of sufficiency of disclosure (Article 83 EPC).

The opposition division decided, that claim 1 of the main request was not novel, but that the grounds for opposition raised by the opponents did not prejudice the maintenance of the patent as amended according to auxiliary request 3 (Article 102(3) EPC).

II. Claim 1 of the main request and of auxiliary request 3 before the opposition division read:

Main request

"The use of cell-free mutant haemoglobin in the manufacture of a non-toxic composition for administration to a patient so as to supplement the oxygen-carrying capacity of the patient's blood, both the alpha and beta chains of said mutant haemoglobin being recombinant polypeptides."

Auxiliary request 3

"The use of cell-free mutant haemoglobin in the manufacture of a non-toxic composition for administration to a patient so as to supplement the oxygen-carrying capacity of the patient's blood, both the alpha and beta chains of said mutant haemoglobin being recombinant polypeptides, and said recombinant alpha chain not being a wild-type or naturally-occurring mutant."

III. Those of the documents which were relied on by the parties and are referred to in the present decision are:

Exhibit (D): Proc. Natl. Acad. Sci., vol.88, (1985), Nagai K., et al., pages 7252 to 7255;

Exhibit (G): PhD thesis of Tame J.R.H., 1989, Chapter 3, pages 26 to 29;

Exhibit (Y): Biotechnology of Blood, (edited by Goldstein J., 1991); Snyder S.R., et al., pages 101 to 116;

Exhibit (AD): US-A-5 563 254;

Document (8): Rev. Fr. Transfus. Hémobiol., vol.35, 1992, pages 407 to 415;

Document (19): Declaration of Dr Charles Scoggin, 13 May 1997;

Document (20): Declaration of Dr Kiyoshi Nagai, 2 August 1999;

Document (21): Declaration of Dr John Olsen, 29 July 1999.

IV. The wording of claim 1 of the requests on file reads as follows:

Main request

Identical to claim 1 of the main request in section II above.

Auxiliary requests 1 and 2

"The use of cell-free mutant haemoglobin in the manufacture of a non-toxic composition for administration to a patient so as to supplement the oxygen-carrying capacity of the patient's blood, both the alpha and beta chains of said mutant haemoglobin being recombinant polypeptides, and the alpha chain component of said haemoglobin being mutant."

Auxiliary request 3 and 4

Identical to claim 1 of auxiliary request 3 in section II above.

Auxiliary request 5

"The use of cell-free mutant haemoglobin in the manufacture of a non-toxic composition for administration to a patient so as to supplement the oxygen-carrying capacity of the patient's blood, both the alpha and beta chains of said mutant haemoglobin being recombinant polypeptides, produced in a cultured bacterial or yeast cell."

V. Oral proceedings were requested by both parties and took place on 11 December 2002 in the absence of appellants II, who were duly summoned but informed the board on 11 October 2002, that they will not attend the oral proceedings.

VI. The submissions by appellants I as far as they are relevant for this decision may be summarized as follows:

When deciding on sufficiency of disclosure in the technical field here at issue, namely recombinant DNA-technology, the boards of appeal in the past had not been considering the volume of a processed product or the degree of development that was necessary for an invention, but only whether the scope of the claims corresponded to the contribution to the state of the art. The disclosure of the invention allowed the haemoglobin (Hb) research community to do meaningful work with fully recombinant Hb for the first time. It had provided a solution to the long-standing problem of obtaining fully recombinant Hb in characterizable quantities for use in an oxygen carrying composition, and for carrying out desired and targeted mutations also in alpha-globin. The economics of processes and products could vary enormously over the lifetime of a patent and were not to be regarded by the EPO when considering sufficiency of disclosure.

VII. The submissions by appellants II as far as they are relevant for this decision may be summarized as follows:

The patent provided a method for producing small amounts of recombinant Hb, which were sufficient only for crystallographic studies and in vitro structural and functional analysis. Large scale production, to yield amounts of Hb which were sufficient for use in compositions such as blood substitutes, was not enabled.

VIII. The appellants I requested that the decision under appeal be set aside and the patent be maintained on the basis of:

claims 1 to 20 of the main request, filed on 5 March 1998;

claims 1 to 20 of the first auxiliary request, filed on 5 March 1998;

claims 1 to 19 of the second auxiliary request, filed on 5 March 1998;

claims 1 to 18 of the third auxiliary request, filed on 5 March 1998;

claims 1 to 17 of the fourth auxiliary request, filed on 5 March 1998;

claims 1 to 20 of the fifth auxiliary request, filed on 4 March 1999.

The appellants II requested that the decision under appeal set aside and that the European patent No. 0 358 708 be revoked.

Reasons for the Decision

The main request
Article 83 EPC

1. Appellants II have objected to the claims under Article 83 EPC, arguing that appellants I claim the use of wholly recombinant Hb for the preparation of a pharmaceutical composition, while the patent is insufficient for enabling the production of the amounts of Hb required for this use.

The European patent must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Sufficiency of disclosure has to be assessed on the basis of the patent as a whole.

2. The invention according to claim 1 is defined as the use of a substance, cell free mutant Hb, for the manufacture of a product, a non-toxic composition, which is intended for a defined purpose, the administration to a patient, to give rise to an desired effect, to supplement the oxygen-carrying capacity of the patients blood. The alpha and beta chains of the mutant Hb are recombinant polypeptides.

The claim thus refers to a method for producing an applicable pharmaceutical product, which upon delivery to a subject in need thereof, produces an effect resulting from the working of its active compound.

3. Hb is the oxygen-carrying component of blood, constructed from four associated polypeptide chains (in the case of Hb A, two alpha-globins and two beta-globins) and bearing prosthetic groups, known as hemes. It circulates through the bloodstream inside the erythrocytes and is able to reversibly bind up to four molecules of oxygen per mole. The oxygen is bound at tissues of high oxygen concentration, as found in the lung, and is released at actively respiring tissues, where the oxygen concentration is low (page 3 of the patent, lines 14 to 28).

4. The skilled person, who is concerned with the development of pharmaceutical products, is aware of the role and mode of operation of Hb as oxygen-carrying component in blood. He is informed, that at the priority date of the present patent, efforts have been made to use Hb solutions as blood substitutes. The

skilled person knows that these solutions, which are prepared from outdated blood, suffer from various disadvantages. They are contaminated with toxic components of the red cell membrane, requiring cumbersome and tedious purification methods, which discouraged large-scale production. They might be contaminated by blood-borne infectious virus, and they have a lower P_{50} as compared to whole blood (page 3, line 53 to page 4, line 4 of the patent cites relevant prior art).

5. Appellants I hold, that the method of claim 1 offers a solution to overcome these disadvantages, by formulating wholly recombinant Hb into a pharmaceutical composition. Recombinant Hb, by definition, is free of cellular debris and blood-borne virus, and due to the possibilities of modification and mutation by genetic engineering techniques, mutants with a P_{50} higher than whole blood can be produced.

6. Although human alpha-and beta-globin genes both have been cloned and sequenced, surprisingly, at the relevant date of the patent, the successful expression of the human beta-globin chain in heterologous cells has been reported only (patent, page 4, lines 27 to 48). Exhibit (D) describes the synthesizing of human beta-globin in E.coli as a cleavable fusion protein, using the expression vector pLcIIFXβ. The produced fusion protein was solubilized, purified and cleaved at the junction by factor X_a. The beta-globin was re-folded in vitro and reconstituted with heme and erythrocyte derived alpha globin to form semi-recombinant Hb (exhibit (D), abstract and materials and methods). According to the patent, the use of pLcIIFXα, wherein the alpha-globin gene has merely been substituted for the beta-globin gene, resulted in negligible expression of the LcII/alpha-globin fusion product.

7. Starting from the teaching in exhibit (D) the patent discloses the construction of vector pLcIIFXβFXα, which encodes a fusion protein consisting of the 31 amino-terminal residues of the lambda phage cII protein, a first factor X_a cleavage site, the 20 amino-terminal residues of human beta-globin, a second factor X_a cleavage site and human alpha-globin at the carboxyl end (Example 1). By using this expression system, plus the one known from exhibit (D), enough recombinant alpha- and beta-globin is expressed to form wholly artificial Hb, wherein both, the alpha- and beta-globin are produced by recombinant DNA technology (page 14, lines 1 to 10).

8. The patent contains detailed information concerning strategies (pages 7 to 9) and methods (Example 2) for increasing the P_{50} of recombinant Hb by site-specific mutagenesis of the coding nucleotides.

9. Example 3 of the patent (page 16, lines 26 to 47) describes the preparation of a blood substitute comprising **60-120 gram/litre** of the produced recombinant Hb.

10. Contrary to other pharmaceutically active compounds, which are efficiently administered to a patient, in **milligram**, or even nanogram doses, Hb when used as a blood substitute is required in relatively large amounts. According to exhibit (Y), page 112, a single dose of blood substitute contains **50 gram Hb**, according to document (8), page 413, it contains **60 gram Hb.**

11. Claim 1 refers to the use of wholly artificial Hb for the preparation of a medicament to supplement the oxygen carrying capacity of the patient's blood.

Although the claim is not restricted to blood substitutes, these are encompassed by its wording, and this embodiment of the invention is the only one substantiated in the description.

12. When considering sufficiency of disclosure of the invention, the board cannot disregard, that for preparation of a composition falling within the scope of claim 1, a specifically large amount of recombinant Hb is necessary. The board comes to the conclusion, that, in order to be sufficiently disclosed, the patent must disclose a method to produce recombinant Hb in the required amount.

13. The patent itself does not contain information concerning the yield of recombinant Hb, and especially of recombinant alpha-globin, produced by the disclosed expression system.

Exhibit (G), the late published doctoral thesis of Jeremy Tame, advised by Dr Nagai, one of the present inventors, gives an indication of the yield of alpha-globin produced by the expression system of the patent. In the passage bridging pages 28 to 29, it is held that with the use of a vector designated pLcIIFXβ83FXα (which according to the appellants I has been redesignated in the patent pLcIIFXβFXα; document (2), page 4), a yield of fusion protein has been produced similar to that of pLcIIFXβ, which was about 2 to 3 times higher than that obtained from pLcIIFXα. Said yield is up to 1 gram of fusion protein from 48 litres of culture. Exhibit (AD), the corresponding US-Patent, contains in column 4, lines 57 58 the following statement: *"The use of the beta header results in about three-fold greater expression of the alpha globin."*

Document (20) holds on page 3 first paragraph, that production runs using clones transformed with pLcIIFXβ, allowed the isolation of 150 to 200 milligram beta fusion protein from 40 litres of culture, which allowed the formation of ca. 30 milligram of reconstituted Hb. In contrast, from a similar fermentation run using pLcIIFXα, only 4 milligram reconstituted Hb were obtained. A few lines down in the middle paragraph of page 3, it is said that, in order to begin crystallization of the protein to make measurements under different conditions, 25 milligram thereof is needed. In a further declaration submitted by appellants I, document (21), it is stressed on page 4, second full paragraph, that a correct interpretation of Figure 3.2 of exhibit (G) showed, that the alpha-globin expression using pLcIIFXβ83FXα was not only 3-fold higher compared to the use of pLcIIFXα, but probably 4- to 5-fold greater.

14. The appellants I point out, that the patent has to be considered to mark a breakthrough in Hb research. It disclosed an expression system, that enabled the skilled person for the first time to produce alpha-globin in an amount that allowed to reconstitute enough wholly artificial Hb to start crystallisation and to perform functional and structural studies of the protein. Once the molecule was available for in vitro studies, all that had to be done for producing amounts necessary for a pharmaceutical use thereof, was to scale up the disclosed production process. The skilled worker would not have been confronted with undue intellectual burden when performing this task.

15. They hold, that the board, when assessing enablement, should not be concerned with the disposable volume of a product, with the degree of development of a process or with economic considerations. In their view this is in line with current case law of the boards of appel. They

referred in this respect to the following decisions: T 456/91 (not published), T 923/92 (OJ EPO, 1996,564), T 296/93 (OJ EPO, 1995,627), T 207/94 (OJ EPO, 1999,273) and T 595/90 (OJ EPO, 1994,695).

16. The board is unable to follow this line of argumentation. Claim 1 does not refer to a recombinant protein or to a method for producing it, but to its use in the manufacture of a pharmaceutical composition, requiring a specifically large amount of the protein. As stated in point 9 above, the patent itself, in Example 3, discloses, that for a central embodiment of the claimed invention, i.e. the use of wholly recombinant Hb for the manufacture of a blood substitute, **60 to 120 gram/litre** of the protein are necessary. According to the state of the art, a single dose of blood substitute, contains **50 gram** (exhibit (Y) page 112) respectively **60 gram** (document (8), page 413) Hb. In case of the $\alpha_2\beta_2$ tetramer of Hb A, half of this amount is made up by alpha-globin.

17. According to exhibit (G), when using pLcIIFXβFXα, the maximum yield of alpha-globin fusion protein was 1 gram per 48 litres. Assuming 100% recovery of processed fusion protein into reconstituted Hb, this method would have to be scaled up 25 to 30 times to obtain one single unit of blood substitute.

18. However, a rate of recovery of 100% is not realistic at all, as can be seen from the calculations in document (20), page 3, first paragraph, where it is said that **150 to 200 milligram** of purified beta-globin allowed the reconstitution of ca. **30 milligram Hb**. This results from the labourious method for processing the expressed fusion protein, as disclosed on page 13 of the patent and in chapter 3 of exhibit (G). The fusion protein, which is precipitated as an inclusion body,

has to solubilized and purified. After cleavage with activated factor X_a it has to be refolded by adding it dropwise to 20 volumes of a folding buffer.

19. The disclosed expression method for the production of alpha-globin fusion protein, yields, according to exhibit (G) 3 times more, according to document (21) five times more, than a method using pLcIIFXα, which according to one of the inventors, allowed the reconstitution of **4 milligram** Hb from 40 litres of culture (document (20), point 6). An amount, which is considered in the patent as "*negligible expression*", not even sufficient to obtain enough protein for crystallographic studies.

20. The calculations in point 8 of document (20), have been disregarded by the board for the following reason: It is stated there, that a fermentation run using pLcIIFXβ83FXα resulted in **500 milligram** of fusion protein, which allowed the reconstitution of **150 milligram** Hb. This is contradictory to the calculations made in point 6 of document (20), and to the figures given in exhibit (G), saying that pLcIIFXβ83FXα yields an amount similar to pLcIIFXβ. The figure of **150 milligram** reconstituted Hb seems to result from a multiplication of **30 milligram** produced by pLcIIFXβ (document (20), point 6), with factor 5, postulated in document (21).

21. Consequently, the board is of the opinion, that the patent discloses a method which allows a skilled person to produce from a 40 litre fermentation run an amount of alpha-fusion protein, that after solubilization, purification, cleavage and refolding, allowed the

reconstitution of **12 to 20 milligram** wholly recombinant Hb (**4 milligram** according to document (20), point 6, multiplied by **factor** 3 (exhibits (G) and (AD)), respectively factor 5 (document (21)).

Claim 1 refers to the use of recombinant Hb in the manufacture of a composition for administration to a patient. A single dose of the only embodiment of the invention that is substantiated in the description, a blood substitute for a human patient, contains **50 000 to 60 000 milligram** Hb (exhibit (Y) and document (8)). The patent in Example 3 describes a blood substitute containing **60 000 to 120 000 milligram** Hb per litre.

Assuming, that half of this amount is made up by alpha-globin, the production process for alpha-fusion protein as disclosed in the patent must be scaled up by a factor of about 1700, for the production of one single dose of blood substitute. This would mean a fermentation volume of about 68 000 litres.

22. The board does not consider the cultivation of bacteria, containing heterologous genes in a biological system, to be expandable ad infinitum in a straightforward manner. Scaling up the method disclosed in the patent for the small scale production of recombinant alpha-globin, in order to obtain an amount of the protein sufficient for one single dose of blood substitute, will confront a skilled person with actual and intellectual undue burden. The patent does not teach how to produce the amounts of recombinant Hb, necessary for the use specified in claim 1.

23. The board does not agree that it can be deferred from the current case law of the boards of appeal, that it has not to be concerned with the disposable quantity of

a product when assessing the enablement of a patent claiming a use of the product which requires a specifically large amount thereof.

24. The following decisions of the boards of appeal, cited by appellants I in this respect (see point 8 above), do not contain such teaching and/or are not applicable in the present case:

The patent underlying the decision T 923/92 (tPA) does not contain a claim referring to the use of a substance for the preparation of a pharmaceutical composition, like present claim 1. T 595/90, referred to by appellants I during the oral proceedings, and T 296/93 are not concerned with the question of sufficiency of disclosure (Article 83 EPC). T 456/91, in point 4 of the reasons for the decision, is concerned with the question, if the invention according to claim 1, referring to a pharmaceutical composition covering an extremely large number of polypeptides, is sufficiently disclosed, if the examples of the patent all relate to a single polypeptide. The question of the disposable quantity of the polypeptides is not touched.

25. Contrary to that, T 207/94 teaches that the question of the disposable amount of a recombinant product, whose use in a pharmaceutical preparation is claimed, has to be discussed when deciding on sufficiency of disclosure. In point 10 of the reasons for the decision, the competent board held, that although larger amounts of beta-IFN could be needed than those produced in an example, it was nevertheless convinced, that the requirements of Article 83 EPC were met, as the description contained sufficient information on how to produce pure interferon in large amounts.

In the present case, neither the examples, nor any other part of the description, contains an enabling disclosure that would allow a skilled person to produce the amounts of wholly recombinant Hb necessary for the claimed use, i.e. for the preparation of a pharmaceutical composition. Therefore, the requirements of Article 83 EPC are not fulfilled.

26. Appellants I repeatedly stressed, that claim 1 is not restricted to the use of recombinant Hb for the preparation of blood substitutes, but that it refers to the manufacture of a non-toxic composition for administration to a patient so as to supplement the oxygen carrying capacity of the patient's blood.

27. It was not disputed that blood substitutes are covered by the claim, but it was stressed that the terminology of claim 1 also applies to other embodiments. Point 4 of document (19), a declaration of the founder of the previous patent proprietor, reads:

"Somatogen also envisaged other oxygen delivery uses for recombinant hemoglobin. Such uses included radiation sensitization and improving oxygen delivery during heart attack, stroke or cardiac catheterization. These indications require less amount of product than would be required for use as a blood replacement therapeutic."

28. Appellants I conclude, that even when assuming that the patent does not teach how to produce enough fully recombinant Hb for use as blood substitute, the requirements of Article 83 EPC are met, as enough protein for uses requiring less amounts can be provided.

29. This opinion is not shared by the board. None of the indications mentioned in document (19) is substantiated or even mentioned in the patent, that, throughout the description, including the examples, refers to the use of recombinant Hb as blood substitute only. The term *"less amount"*, used in combination with these indications, is not clear and open to interpretation. No exact data, clarifying the exact amounts of recombinant Hb necessary for these uses, have been provided by appellants I. The board, considering the mode of operation of Hb as oxygen-carrying component of blood, which, different from substances like receptors, antibodies or hormones, requires relatively large amounts of the protein in order to arrive at the desired therapeutic effect, has no information available, that amounts of Hb, lying in the range of what is obtainable by the method disclosed in the patent, are sufficient for the production of a pharmaceutical composition for one of the indications mentioned in document (19).

30. Hb, whether fully recombinant or of natural origin, is responsible for the transport of oxygen in blood, and thus, supplements the oxygen carrying capacity of blood. When used for the production of a pharmaceutical composition to achieve this desired therapeutic effect in a patient, it has to be provided in amounts, for whose production the patent does not disclose a method in a way sufficiently clear and complete for it to be carried out by a person skilled in the art.

31. The board therefore concludes, that claim 1, and the request of which it is part, are not allowable under Article 83 EPC.

Auxiliary requests 1 to 5

32. As the above reasons for claim 1 of the main request apply in the same way to claim 1 of all five auxiliary requests, they are also not allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey