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DECISION
of 22 April 2004

Case Number: T 0395/00 - 3.3.4

Application Number: 91913972.5

Publication Number: 0495047

IPC: A61K 38/42

Language of the proceedings: EN

Title of invention:

Stable hemoglobin based composition and method to store same

Patentee:

BAXTER INTERNATIONAL INC.

Opponents:

Fresenius AG
Hemosol, Inc.

Headword:

Stable hemoglobin compositions/BAXTER

Relevant legal provisions:

EPC Art. 54, 56, 83, 114, 123(2)

Keyword:

"Late-filed documents - admission into proceedings - (no)"
"New argument - admission into proceedings - (yes)"
"Added matter - (no)"
"Sufficiency of disclosure - (yes)"
"Novelty - (yes)"
"Inventive step - (yes)"

Decisions cited:

G 0001/95, G 0007/95, T 0092/92, T 0612/92, T 0634/92,
T 0745/92, T 1002/92

Catchword:

-



Case Number: T 0395/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 22 April 2004

Appellant I:
(Opponent 02)

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Respondent:
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Decision under appeal:

Decision of the Opposition Division of the
European Patent Office posted 17 March 2000
rejecting the oppositions filed against
European patent No. 0495047 pursuant to Article
102(2) EPC.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: G. L. Alt
G. E. Weiss

Summary of Facts and Submissions

I. An appeal was lodged by opponent 02 (appellant I) and opponent 03 (appellant II) against the decision of the opposition division whereby the oppositions were rejected and the European patent No. 0 495 047 which had been opposed under Article 100(a) EPC (lack of novelty, lack of inventive step) and Article 100(b) EPC and Article 100(c) EPC, was maintained unamended on the basis of claims 1 to 7 as granted according to Article 102(2) EPC.

Independent claims 1, 2, 4 and 7 read as follows:

"1. A method of preparing a hemoglobin based composition having methemoglobin in an amount not greater than 15% of total hemoglobin, wherein the composition may function as an oxygen carrying solution upon administration to a patient, the method comprising removing oxygen from an oxygen impermeable container, adding a purified substantially deoxygenated hemoglobin solution to the container and storing the container at a temperature of 5°C to 45°C for a sufficient time to permit autoreduction of methemoglobin."

"2. A method of reducing methemoglobin in a solution of substantially deoxygenated and purified methemoglobin, the method comprising removing oxygen from an oxygen impermeable container, adding the deoxygenated and purified hemoglobin solution to the container, and storing the container at a temperature of 5°C to 45°C for a sufficient time for autoreduction of methemoglobin in the solution to occur, such that the resultant solution contains methemoglobin in an amount

not greater than 15% of total hemoglobin, so that the solution may function as an oxygen carrying solution upon administration to a patient."

"4. A method of storing hemoglobin for use as an oxygen carrying solution upon administration to a patient, the method comprising
purging an oxygen impermeable container with nitrogen,
deoxygenating a purified hemoglobin solution,
filling the oxygen-purged impermeable container with an aliquot of the deoxygenated, purified hemoglobin solution,
sealing the container,
storing the container for a sufficient time to permit scavenging of residual oxygen from the hemoglobin solution,
storing the container further at a temperature of 5°C to 45°C to permit autoreduction of methemoglobin to a level not greater than 15% of total hemoglobin, and further storing the hemoglobin solution between -270°C and 45°C."

"7. A method for packaging a hemoglobin solution, comprising purging an oxygen impermeable container with nitrogen,
preparing a thoroughly deoxygenated, purified hemoglobin solution,
filling said purged container with an aliquot of said thoroughly deoxygenated, purified hemoglobin solution, and
sealing the container,
whereby methemoglobin in the solution is autoreducible to a level not greater than 15% of the total hemoglobin

when the sealed container is stored at a temperature of 5°C to 45°C for a sufficient amount of time to permit autoreduction to said level such that the solution is usable as an oxygen carrying solution upon administration to a patient."

II. With the statement of the grounds of appeal appellant I submitted *inter alia* a new objection under Article 123(2) EPC and a new objection of lack of novelty based on newly filed document D23. Appellant II submitted documents D21 and D22.

III. In reply to the statements of grounds of appeal the respondent (patentee) filed written submissions in which he *inter alia* argued against the introduction of D23 and the new objection under Article 123(2) EPC.

IV. Oral proceedings were held on 22 April 2004 in the absence of appellant I who had notified the board before that he would not attend oral proceedings.

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

D1: WO-A-89/06969

D3: Di Iorio, E. "Preparation of derivatives of ferrous and ferric hemoglobin", *Methods in Enzymology*, 1981, vol. 76, pages 57 to 72

D5: US 4,831,012 (American equivalent of D1)

D6: Schmukler, R. et al., "Rapid deoxygenation of red cells and hemoglobin solution using hollow

capillary fibers", *Biorheology*, 1985, vol. 22, pages 21 to 29

- D9: Antonini, E. et al., "Hemoglobin and myoglobin in their reactions with ligands": Chapter 1: "Preparation and some general properties of hemoglobin and myoglobin", 1971, pages 1 to 6 and Chapter 2: "The derivatives of ferrous hemoglobin and myoglobin" pages 13 to 15
- D11: DeVenuto, F., "Stability of hemoglobin solution during extended storage", *Journal of laboratory and Clinical Medicine*, 1978, vol. 92, pages 946 to 952
- D18: Jacobs, J., "Preservation of human hemoglobin solutions without methemoglobin formation", *American Physiological Society*, 54th Annual Meeting, 1942, pages 42 to 43
- D19: Morell, S. et al., "Deoxygenation of hemoglobin in closed cuvettes", *Physiological Chemistry and Physics*, 1970, vol. 2, pages 467 to 476
- D23: US 4,826,811

VI. The arguments of the parties may be summarized as follows:

Admissibility of late-filed documents into the proceedings (Article 114 EPC)

Respondent

Document D23 had not been introduced in order to supplement a point that was originally made, but was used for a new argument. Therefore it was not admissible.

Appellant II

Appellant II submitted that he did not intend to rely on document D23 which had been introduced by appellant I.

Admissibility of the new argument under Article 123(2) EPC

Respondent

The objection of appellant I under Article 123(2) EPC was new. Submissions in relation to Article 123(2) EPC were usually independent and self-contained and not interrelated like for example arguments in relation to prior art. Consequently, decisions G 1/95 and G 7/95 had to be construed such that the patentee's consent was necessary with regard to a new argument under Article 123(2) EPC. This consent was however not given.

Appellant II

Article 123(2) EPC was not a fresh ground of opposition because it had been mentioned in the notice of opposition of the then opponent 03. The submission under Article 123(2) EPC was a new argument only for which patentee's consent was not necessary.

Amendments (Article 123(2) EPC)

Appellants I and II

The claims of the application as filed did not refer to a method comprising explicitly as a first step the removal of oxygen from the oxygen impermeable container. The application as originally filed taught on the one hand on page 3, last paragraph that no oxygen removal from the container was necessary and on the other hand on pages 6 to 7 that oxygen had to be removed rigorously in a very specific way. Claims 1 and 2 of the patent in suit referred to the removal of an non-specific amount of oxygen. This was an intermediate generalisation which was not originally disclosed.

Claim 1 was directed to making a hemoglobin solution starting with a deoxygenated solution. The original application made a distinction between making a hemoglobin solution with an a methemoglobin content of less than 15% and its subsequent storage. In the original application there was however no disclosure of the use of a deoxygenated solution in the context of making hemoglobin.

Respondent

The concept to eliminate as much oxygen as possible was clear to the reader of the application and that the specific measures for oxygen removal disclosed on pages 6 and 7 were only one way of how this could be achieved.

The application always disclosed the deoxy-form for making hemoglobin.

Sufficiency of disclosure (Article 83 EPC)

Appellants I and II

The method described in Examples 1 and 4 of the patent in suit had all the features of the claims. However, it did not result in a hemoglobin solution with a methemoglobin content of less than 15%. This was an indication that the claimed method did not reliably lead to the desired methemoglobin content.

The methods of Examples 2 and 5 only differed from those of Examples 1 and 4 in that more efforts were taken to remove oxygen. "Efforts" were however not a technical feature. Therefore a skilled person did not know which sort of efforts and how much he should use in order to operate the method successfully.

Document D11 disclosed a method within the definition of the claims of the patent in suit. Nevertheless the methemoglobin content increased. This was another proof that the method did not work

The terms in the claims "removing oxygen", "purified substantially deoxygenated" and the temperature range of 5°C to 45°C were so vague that it was not plausible that the method could be carried out under all the conditions encompassed by the claims. Tables 5 and 6 demonstrated, for example, that at 5°C autoreduction did not occur. Consequently it was an undue burden to

find out those conditions under which the method reliably worked.

Respondent

Examples 1 and 4 were not within the scope of the claims, but they taught in combination with Examples 2 and 5 the importance of excluding oxygen.

The process of document D11 was not within the definition of the claims, because oxygen was not removed from the container before the addition of the hemoglobin solution.

Appellant II's submission that the invention could not be carried out over the whole claimed range remained speculation because he had not submitted evidence.

Tables 5 and 6 demonstrated that the method was successful because the methemoglobin content did not increase.

Novelty (Article 54 EPC)

Appellants I and II

The term "purified hemoglobin solution" extended to solutions with any level of purification and not only to enzyme-free solutions. Therefore, Example 6 of documents D1/D5 disclosed a method comprising each feature of claims 1, 4 and 7 and therefore their subject-matter was not novel.

Document D18 started with a hemoglobin solution purified by Seitz filtration which removed microorganisms and any particulate matter like membranes together with membrane-bound enzymes. Table 8 of the patent showed that the hemoglobin solution of the patent in suit was not completely free of oxidation protecting enzymes. Consequently, the Seitz-filtrated hemoglobin solution of document D18 was purified in the sense of the patent in suit. Since the remaining process steps of document D18 were equivalent to those of the claims, document D18 was novelty-destroying.

Respondent

The most important difference between documents D1/D5 and document D18 and the claimed method was that the former did not disclose removal of oxygen prior to addition of the hemoglobin solution.

Inventive step (Article 56 EPC)

Appellant I

Document D3 was the closest prior art. This document already disclosed that the best way of storing hemoglobin was in the deoxygenated form in the absence of oxygen. The document only stated that there were technical difficulties in keeping the solution completely oxygen free. If a problem could be formulated at all in view of document D3, it was to provide the technical means to solve these difficulties. Apparatuses suitable to overcome these difficulties were mentioned in document D1 or document D6.

Appellant II

Document D1, the closest prior art document, disclosed in Example 6 that purified, deoxygenated hemoglobin solutions were stable under vacuum when heated at a temperature of 45 - 85°C. The problem underlying the patent in suit was how to store the hemoglobin solution of document D1. Document D9 disclosed that deoxygenated, purified hemoglobin solutions could be stored in the cold under vacuum or under an inert gas. Document D19 disclosed the anaerobic transfer at room temperature of a practically pure hemoglobin solution into cuvettes which had been flushed with nitrogen. Moreover D19 suggested that reversible autooxidation occurred which was equivalent to a disclosure of autoreduction. Thus document D9 in combination with document D19 disclosed all the essential features of the claimed method.

The subject-matter of the claims was also obvious in view of a combination of document D1 with document D18 disclosing directly that when a purified hemoglobin solution was deoxygenated and sealed *in vacuo* in glass ampoules and stored at room temperature no methemoglobin formation occurred for periods of up to three months.

Respondent

Document D3 was not the closest prior art because it did not relate to the preparation of hemoglobin solutions for use in patients, but in functional

studies. Therefore, the hemoglobin solution was not purified in the sense of the patent.

Document D1 did not address the problem of storage but dealt with purification of hemoglobin solutions and the inactivation of viruses. Nevertheless it may be regarded as the closest prior art document because solutions that were prepared for clinical purposes must obviously be stored.

Document D1 itself did not refer to the stability of the hemoglobin solution during storage, but only during the heating process which only lasted a few hours.

Document D9 sought to examine the reaction of hemoglobin and myoglobin with their ligands and therefore dealt only with the short-term storage of hemoglobin solutions for scientific purposes. This period was not sufficient for storage for clinical purposes. Even if a person skilled in the art had turned to document D9, it taught either storage of hemoglobin in its oxy-form for several weeks in the cold or as deoxygenated hemoglobin in the cold *in vacuo* or under an inert gas.

Document D18 was too old in order to provide a solution to the problem of storing purified hemoglobin solutions.

D19 was a study about the equilibrium between oxy- and deoxyhemoglobin and used oxyhemoglobin for transfer into the cuvettes. Therefore, the process was not comparable to the claimed method. Moreover, the term

"reversible autooxidation" in document D19 was not equivalent to autoreduction in the sense of the patent.

VII. Requests

The appellants - appellant I in writing and appellant II during the oral proceedings - requested that the decision under appeal be set aside and that the European patent No. 0 495 047 be revoked.

The respondent requested that the appeals be dismissed and that the patent be maintained as granted (main request) or, in the alternative, that the patent be maintained in amended form on the basis of claims 1 to 11 as granted with the correction under Rule 88 EPC of claim 2 as requested in the letter filed on 19 October 1999 (first auxiliary request) or on the basis of claims 1 to 11 in the auxiliary requests 1 and 2 filed on 19 October 1999 (second and third requests).

He furthermore requested non-admittance into the proceedings of the new argument of opposition under Article 123(2) EPC of appellant I and of document D23.

Reasons for the Decision

Admissibility of late-filed documents into the proceedings (Article 114 EPC)

1. In accordance with Article 114(2) EPC the boards of appeal are empowered to disregard facts or evidence which are not submitted in due time. It is established

case law that in appeal proceedings new facts and late-filed evidence should only very exceptionally be admitted if the material is *prima facie* so highly relevant so as to prejudice the maintenance of the patent in suit (see eg decision T 1002/92, EPO OJ 1995, 605, point 3.4 of the reasons.)

2. None of documents D21 to D23 has a bearing on the decision to be taken. This is especially true for document D23 which was used for a new objection of lack of novelty. The subject-matter disclosed therein differs in at least one feature from the claimed subject-matter: Oxygen is not removed from the container **before** the hemoglobin solution is added.
3. Therefore, none of documents D21 to D23 is allowed into the proceedings pursuant to Article 114(2) EPC.

Admissibility of the new argument under Article 123(2) EPC

4. The respondent submitted that decisions of the Enlarged Board of Appeal G 1/95 and G 7/95 (EPO OJ 1996, 615; EPO OJ 1996, 626) should be construed such that patentee's consent must be obtained in relation to a totally new argument under Article 123(2) EPC even if part of the original opposition was made under Article 100(c) EPC.
5. A ground of opposition constitutes the legal basis for objecting to the maintenance of a patent.
6. Decisions G 1/95 and G 7/95 deal with cases where fresh grounds of opposition were introduced at the appeal stage. According to these decisions a ground is to be considered as "fresh" if it was neither raised nor

substantiated in the notice of opposition nor was it introduced into the proceedings by the opposition division (see point 5.4 of the reasons of G 1/95). Hence, a fresh ground represents a new legal basis for an objection.

7. In the present case Article 123(2) EPC was raised as a ground of opposition and substantiated in the original notice of opposition of opponent 03 (now appellant II). The opposition division decided on this issue in its written decision. Therefore, following decisions G 1/95 and G 7/95, Article 123(2) EPC is not a fresh ground in these proceedings.
8. The board cannot identify in the two decisions cited, either generally or for the specific case of Article 123(2) EPC, a suggestion on how to proceed with new arguments in relation to already existing grounds of opposition. Therefore, the respondent's argumentation is not convincing.
9. A further question is whether there is another legal basis in the EPC for rejecting late arguments. Article 114(1) EPC applies in all proceedings before the EPO, though, due to their judicial and therefore less investigative nature, in a more restricted form in appeal proceedings. This requires that within the legal framework established by the parties, the boards consider all facts presented by the parties and decides which of them are crucial for the decision to be taken. In view of Article 114(1) EPC during the decision-making process "facts and evidence" on the one hand and "arguments" on the other hand are taken into account.

10. Article 114(2) EPC is a limitation on the obligation under Article 114(1) EPC in that it permits to exclude from the proceedings facts and evidence which are not submitted in due time. In contrast to Article 114(1) EPC, Article 114(2) EPC does not refer to "arguments".

11. The new attack under Article 123(2) EPC by appellant I does not constitute facts or evidence. In the case of amendments the "fact" is the amendment as such. "Evidence" for amendments is the submission of new pages comprising the amendment. Both events have taken place in due time. According to decision T 92/92 (dated 21 September 1993; point 2, paragraph 3 of the reasons) arguments may be understood "to include the parties' submissions as to the consequences that result from applying the law to the facts and evidence." Thus, the new attack represents a new argument.

12. Since Article 114(2) EPC is not a legal basis for disregarding late arguments, the argument is taken into consideration.

Amendments (Article 123(2) EPC)

13. According to Article 123(2) EPC a European patent application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. This requires examination as to whether an amendment results in the introduction of information which the skilled person cannot derive directly and unambiguously, either explicitly or implicitly, from the originally presented application documents.

14. Appellant II contends that the original application documents do not contemplate using deoxygenated hemoglobin in the context of making the hemoglobin solution, but only in the context of its storage. Therefore, he considers the expression in claim 1 "adding a purified substantially deoxygenated hemoglobin solution to the container" not to be supported by the original application documents.

15. Claim 4 of the application documents as originally filed relates to "a method to prepare a hemoglobin based composition comprising:
 - a) adding a purified hemoglobin solution to an oxygen impermeable container, and
 - b) storing said container at a temperature of about 5°C to about 45°C for a sufficient time to permit autoreduction of sufficient methemoglobin for the composition to function as an oxygen carrying solution upon administration to a patient."

16. Example 4 of the application as filed discloses undeoxygenated hemoglobin solution as a starting material. All the other seven examples use a deoxygenated solution. Thus, the reader of the application underlying the patent in suit understands that both possibilities are referred to. The restriction of the subject-matter of claim 1 to one of these directly derivable possibilities does not contravene Article 123(2) EPC.

17. The second issue under Article 123(2) EPC is whether a reader of the claims 1 and 2 of the patent in suit would interpret the expression "removal of oxygen from an oxygen impermeable container" broadly as

encompassing the removal of a non-specific amount of oxygen and thus including the possibility of removing only a small amount. This would however according to appellant II not be supported by the application documents as originally filed.

18. The application stresses in several passages the importance of removing oxygen completely, for example in Examples 2 and 6 (corresponding to Examples 2 and 5 of the patent in suit).
19. Since a claim is not read in isolation, but always in the context of the complete application, the skilled reader would not construe the above cited expression such that it related also to the partial removal of oxygen, but rather that the complete removal by any suitable means - for example flushing with nitrogen - was necessary for successfully carrying out the method.
20. The board is convinced that the amended passage would be interpreted by the skilled reader in this sense in view of the application documents as a whole and as originally filed and thus it cannot be regarded as added matter.
21. The requirements of Article 123(2) EPC are fulfilled.

Sufficiency (Article 83 EPC)

22. In the assessment as to whether a European patent application fulfils the requirement of Article 83 EPC, it is an established principle in the case law of the boards of appeal that, for the disclosure of an invention to be sufficiently clear and complete, the

skilled person, on the basis of the information provided in the application itself and by using the common general knowledge at the application date (or priority date, as the case may be), has to be able to achieve the desired result without undue burden and without exercising inventive skill (see eg decisions T 694/92, OJ EPO 1997, 408 and T 612/92, dated 28 February 1996).

23. An objection of lack of disclosure can only be successful if the party alleging lack of sufficient disclosure substantiates its doubts by tangible evidence. Such evidence could for example come in the form of experiments demonstrating that the exact repetitions of the conditions of an example of a patent falling under the scope of the claim do not lead to the desired result.
24. It was argued that Examples 1 and 4 of the patent in suit as well as document D11 disclose a method which is identical to the claimed one, but that the methemoglobin content of the hemoglobin solution did nevertheless not fall to less than 15%.
25. It is true that at first sight the method of Example 1 of the patent in suit seems to have all the features of the claimed method. However, this impression is shifted once this example is considered in the context of Example 2. In Example 1 the inventors express discontent with the experimental conditions: "Despite the efforts to exclude oxygen, the sample initially contained 20% oxy diaspirin". Example 2 begins with a statement reflecting the wish to change the experimental set-up: "In this experiment efforts were

- taken to ensure that the samples were stored in sufficiently oxygen impermeable containers to observe autoreduction". It can be inferred from these statements that the inventors consider that the method of Example 1 was not carried out adequately because oxygen was not sufficiently excluded. Consequently, the combination of Example 1 and 2 conveys that Example 1 does not reflect the claimed method.
26. Similar conclusions can be drawn for Example 4 which has to be considered in combination with Example 5. Example 5 discloses that the same technology as in Example 4 was used, but that rigorous efforts were taken to remove oxygen from the isolator, the container and the hemoglobin solution. Thus, the method as carried out as in Example 4 is not within the scope of the claimed method.
27. In this context it is also noted that the board cannot follow appellant II arguing that the skilled person was left without guidance as to the manner and extent of efforts to be taken in order to modify Example 1 and 4 such that a methemoglobin content of less than 15% was achieved. Example 2 specifies that the efforts concentrated on the containers (see above). Example 5 explains that "rigorous efforts were employed to purge oxygen from the isolator, the packing containers and the hemoglobin solution. After fogging, the isolator was purged with low-oxygen grade nitrogen. The purge line was then switched to ultra-pure nitrogen with an in-line oxygen trap and the isolator was purged further. All components were carefully purged with the same ultra-pure nitrogen." Thus, the skilled person is given information about what to do in case of failure.

28. Document D11 deals with the stability of a stroma-free hemoglobin solution during extended storage. Some experiments involve storage under vacuum or under nitrogen: An aliquot of hemoglobin solution is placed in a glass ampoule and evacuated and then refilled with oxygen-free nitrogen. The complete procedure is repeated three times. Then the ampoule is sealed after a final evacuation or after refilling with nitrogen. Although this disclosure is *prima facie* very similar to the claimed procedure, it differs however in at least one essential aspect, namely in that oxygen is not removed from the ampoule prior to adding the hemoglobin solution. Consequently, the method of document D11 is not the same as the claimed method and therefore lacks evidential weight.
29. Thus, neither Examples 1 and 4 nor document D11 are appropriate to call in question the sufficiency of disclosure of the patent in suit.
30. Moreover, it was submitted that some terms of claim 1 were so broad that it was implausible that the method could be carried out successfully over the whole breadth of the claim. The main evidence brought forward in support of this argument relates to the fact that on the one hand 5°C was the lowest temperature value in the claimed method whereas on the other hand Tables 5 and 6 of the patent in suit showed that at 5°C autoreduction did not take place.
31. However, the iron atom in the middle of the four heme prosthetic groups of the hemoglobin molecule is the site of oxygen binding and release. In order to

maintain this reversible oxygen binding capability, the heme iron must be in the Fe^{2+} state. When a solution of hemoglobin is stored for longer periods, the iron tends to oxidize to the Fe^{3+} state, giving the methemoglobin form which does not reversibly bind oxygen and is therefore physiologically ineffective.

32. The claimed method relies on the discovery that under a certain set of conditions an auto-reduction reaction occurs that spontaneously converts the methemoglobin in the solution to the physiological Fe^{2+} hemoglobin. After the auto-reduction of methaemoglobin has occurred the solution can be stored for a long time even at room temperature.
33. Table 5 shows data about the methemoglobin content in a hemoglobin solution. At 25°C the methemoglobin level increases on day 1 and then decreases until the end of surveying on day 56. At 5°C this trend is not visible, but a small increase and decrease of the methemoglobin content alternate with each other. Table 6 shows a similar phenomenon with the additional complication that at day 59 the measuring apparatus was changed and overall higher values are obtained. But, indeed both tables seem to demonstrate at first sight, that the methemoglobin content in the solution has not decreased to less than 15% after the same number of days at 5°C compared to 25°C . This is however no proof that auto-reduction does not occur and that therefore the claimed method does not work at 5°C because, if this was the case, a steady increase of methemoglobin would be observed. In the board's view the data may indicate that at 5°C auto-reduction takes longer to start. Indeed, the patent specification discloses at the top of page 4

that the autoreduction reaction is accelerated at higher temperatures and on page 5 at the bottom that during storage at 5°C autoreduction is very slow.

34. Thus it is concluded that the objections of the appellants as to the insufficiency of disclosure were not substantiated by convincing evidence. Consequently, the requirements of Article 83 EPC are fulfilled.

Novelty (Article 54 EPC)

35. It was submitted that the subject-matter of claims 1 to 5 and 7 lacks novelty in view of Example 6 of documents D1/D5. The documents relate to a method for preparing purified hemoglobin solutions. For this purpose the deoxygenated hemoglobin solution is heated typically at a temperature 60°C for 10 hours. This procedure selectively inactivates viruses and removes non-hemoglobin proteins while the hemoglobin remains stable and retains its biological activity.
36. The method of documents D1/D5 differs from that of the patent in at least the characteristic that the container is not - as required by claims 1, 2, 4, 7 - made oxygen-free before the hemoglobin solution is added. Consequently, for this reason alone document D1 or D5 does not anticipate the subject-matter of the claims.
37. Moreover, appellant I considers document D18 as novelty-destroying for the subject-matter of claims 1 to 4. Document D18, an abstract from 1942 reads as follows: "Human haemoglobin solutions made isotonic with blood plasma are sterilized by Seitz filtration.

The solutions are completely reduced by vacuum extraction with a Hyvac pump. They are then sealed *in vacuo* in glass ampoules. Although exposed to light and warm room temperatures these solutions show no methaemoglobin formation for periods up to three months." A comparison of this disclosure with the claimed method reveals that, like in document D1 or D5, there is no removal of oxygen from the glass ampoules before the haemoglobin solution is added. Therefore, document D18 cannot be novelty-destroying for the subject-matter of the claims.

38. Consequently, novelty of the subject-matter of the claims is acknowledged. The requirement of Article 54 EPC is fulfilled.

Inventive step (Article 56 EPC)

39. *In vivo* the heme iron is continuously oxidized leading to methemoglobin formation. The red blood cells contain, however, a number of enzyme systems that either reduce the methemoglobin or eliminate activated oxygen products such as superoxide that can also oxidize heme iron. Therefore, less pure preparations of hemoglobin that still contain a considerable amount of these enzymes are more resistant against oxidation during storage. However, since contaminating proteins may cause toxic or immunogenic reactions in patients, it is desirable to use hemoglobin solutions for administration to patients that are almost free of these contaminating proteins. Due to the lack of the protective enzymes however, the heme iron in these solutions is more easily oxidized leading quickly to an undesirably high methemoglobin content. Thus, these

- purified preparations quickly lose their biological activity during storage.
40. Oxidation in pure and less pure hemoglobin solutions is even more accelerated at room temperature. Therefore such solutions are usually stored refrigerated or frozen. This is however inconvenient because these solutions cannot be immediately administered to patients - which in medical emergency situations can be a life-saving measure. Moreover, storage at room temperature has the further advantage to prevent mistakes by inappropriate thawing or damage to the solution by inadvertent unrefrigeration. Finally, hemoglobin preparations which are stable at room temperature are easier to handle during transportation.
 41. The patent in suit deals with the specific problem of preserving highly **purified** hemoglobin solutions at room temperature.
 42. In accordance with the case law the closest prior art for objectively assessing inventive step is generally that which aims at the same purpose and having the most relevant technical features in common.
 43. In view of this case law document D3, suggested by appellant II as the closest prior art, is not suited because it does not deal with the same purpose as the patent in suit, i.e. the storage of **purified** hemoglobin solutions (see section 48 below).
 44. Document D1, suggested by appellant II as the closest prior document, does not explicitly address the problem of storage of purified hemoglobin solutions, but deals

with their preparation. The purification-method of document D1 is mentioned in the patent in suit as one possibility of obtaining the starting material of the claimed method (see page 4, lines 33 to 34). The document mentions on page 7 that hemoglobin solutions are usually stored cold or frozen to avoid oxidation. In the board's view a person skilled in the art would infer from this general statement that this applies to the solutions prepared in document D1 as well. Thus, although not dealing with storage, the board considers document D1 as the most suitable starting point because once one has prepared a highly purified hemoglobin solution it is evident that it must be stored.

45. In view of document D1 the problem underlying the patent in suit is to provide means for making and storing a purified hemoglobin composition with less than 15% methemoglobin which is stable against oxidation during storage at convenient temperatures.

The solution to this problem is a set of conditions which are described in claims 1, 2, 4, 7.

Examples 2, 3, 5, 6 demonstrate that the claimed method solves the above formulated problem.

46. The question to be answered for the evaluation of inventive step is whether there is prior art which alone or in combination renders this solution obvious.
47. It has been argued that it was evident in view of the hemoglobin stability during heating at 60°C disclosed in document D1 that hemoglobin could be stored at ambient temperature. In the board's view this

conclusion cannot be drawn. Firstly, the solution heated in document D1 is not purified in the sense of the patent. On the contrary, it is the purpose of the method to prepare such a solution. Secondly, the heating process requires stability only for a shorter period. Thus, document D1 alone does not give a hint to apply the claimed method as a solution to the above formulated problem.

48. The appellants were furthermore of the opinion that document D3, document D9, document D11, document D18 and document D19 contained pointers to the solution provided by the patent in suit.
49. However, as far as documents D3, D11 or D18 are concerned, none of them refers to highly purified hemoglobin solutions. Document D3 discloses the preparation of derivatives of hemoglobin for scientific use and sets out in its first paragraph that "preparation of the different derivatives can often be done directly from the hemolysate without any further purification. This is justified by the fact that hemoglobin is the major proteic component of the erythrocytic cytoplasm". The assays of document D11 are carried out with hemoglobin purified by filtration through a 0.22 μm filter or by crystallisation. Both methods mainly remove membrane components. Although a small percentage of the protective enzymes is membrane-bound, the greater amount is soluble and remains in the filtrate giving rise to a less purified hemoglobin solution. Document D18 uses a Seitz-filtrated hemoglobin preparation. As well as the methods of document D11, this method only removes particulate matter with the respective consequences on purity of

the solution. Since none of these documents relates to highly purified hemoglobin solutions, a person skilled in the art being aware of the specific problems involved with them, would not have expected to get any helpful advice from these documents for solving this specific problem. Therefore, he would not have combined any of them with the closest prior art document in order to solve the problem underlying the patent in suit.

50. In decision T 745/92 (dated 8 June 1994) the board sets out that "when assessing inventive step, the disclosures of two prior documents (...) may only be combined so as to result in a finding of lack of inventive step in a claimed invention if, on an objective assessment, it would have been obvious for a skilled person, when seeking to solve the problem underlying the claimed invention but without knowledge of the claimed solution to that problem, so to combine them." Analogously, the board finds in the present case that a person skilled in the art starting from document D1 and seeking a method to make and stably store a purified hemoglobin composition with less than 15% methemoglobin at convenient temperatures would not have taken any of these documents into consideration at all and that therefore, they do not render the claimed invention obvious.

51. Document D9 is a general textbook about hemoglobin and myoglobin in their reaction with ligands. It describes methods for preparing hemoglobin with different degrees of purity. In the short chapter about storage no distinction is made between the purified or less purified hemoglobin. It is generally suggested that the

best way of storage for several weeks is in the form of oxyhemoglobin in the cold or as deoxyhemoglobin *in vacuo* or under an inert gas in the cold. The document is not only silent about specific process steps or the methemoglobin content, but also it does not give an indication that deoxyhemoglobin could be stored at ambient temperatures.

52. Document D19 is a study about the equilibrium of oxyhemoglobin and deoxyhemoglobin in closed cuvettes and does not touch on the subject of storage. If a person skilled in the art had taken this document into account at all, all that it could take from it would be that, when oxyhemoglobin is transferred anaerobically into cuvettes that were flushed with nitrogen before and which are tightly stoppered after transfer, the oxyhemoglobin is transformed to deoxyhemoglobin. Thus, not only is oxyhemoglobin used as a starting material, but also there are no indications about the methemoglobin level during this manipulation.
53. During the deoxygenation reaction of oxyhemoglobin free oxygen is created. Document D19 suggests that oxygen may be consumed by the system by "reversibly autooxidating hemoglobin". The authors speculate that SH-groups could be involved in this reaction. It has been argued that this amounted to the description of the autoredox reaction which is the underlying chemical mechanism of the present invention. In the board's view this disclosure in document D19 is ambiguous because it could not only relate to the oxidation of the heme iron, but also to oxidation of the SH-groups to an S-S group. Consequently,

document D19 is not considered to disclose
autoreduction in the sense of the patent in suit.

54. Hence, none of the documents renders the subject-matter
of claim 1 obvious. Independent claims 2, 4, and 7 all
refer to the features considered inventive in claim 1
and thus the respective reasons apply. Consequently,
the subject-matter of all claims involves an inventive
step.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey