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D E C I S I O N
of 18 November 1998

Case Number: T 0919/93 - 3.3.4

Application Number: 83104642.0

Publication Number: 0094611

IPC: A61K 35/16

Language of the proceedings: EN

Title of invention:
A method for the heat treatment of plasma or plasma fractions and compositions obtained thereby

Patentee:
Cedars-Sinai Medical Center

Opponents:
Central Blood Laboratories Authority 'The Crest'
Pharmacia Aktiebolag
Rorer Group, Inc.
Yamada, Hideo

Headword:
Heat treated Factor VIII/CEDARS-SINAI MEDICAL CENTER

Relevant legal provisions:
EPC Art. 53a, 54, 56, 83

Keyword:
"Main and first auxiliary request: novelty (no)"
"Second auxiliary request: inventive step (no)"
"Third auxiliary request: sufficiency of disclosure (no)"

Decisions cited:

T 0449/90, T 0012/81, T 0181/82, G 0010/91, T 0952/92

Catchword:

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Case Number: T 0919/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 18 November 1998

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 16 August 1993 concerning maintenance of European patent No. 0 094 611 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
C. Holtz

Summary of Facts and Submissions

I. European patent No. 0 094 611 with the title "A method for the heat treatment of plasma or plasma fractions and compositions obtained thereby" was granted with 5 claims, based on European patent application No. 83 104 642.0 filed on 11 May 1983 and claiming a priority of 13 May 1982 (US 377863).

II. Oppositions were filed by Opponents (O1) to (05) on the grounds of Articles 100(a), 100(b) and 100(c) EPC, i.e. lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC), insufficiency of disclosure (Article 83 EPC) and added subject-matter (Article 123(2) EPC). Opponent (01) withdrew the opposition.

III. The Opposition Division revoked the patent on the grounds of added subject-matter (Article 123(2) EPC) and insufficiency of disclosure (Article 83 EPC). Because of these deficiencies, the Opposition Division considered it not to be necessary to take position with regard to the objections under Article 100(a) EPC and with regard to the validity of the claims to priority.

IV. An appeal was filed by the Patentee. In decision T 449/90 of 5 December 1991, Board 3.3.2 held that the claims satisfied the requirements of Article 123(2) EPC and 83 EPC and remitted the case to the Opposition Division for further prosecution.

V. By its decision dated 16 August 1993, the Opposition Division, while denying the inventive step of claim 2

of the main request, concluded that the claims of the first auxiliary request filed at the oral proceedings of 16 December 1992 satisfied the requirements of the EPC.

Claim 1 of the first auxiliary request read as follows:

"1. An AHF enriched composition for the manufacture of a medicament agent for the treatment of the bleeding disorders; said composition comprising a human Factor VIII concentrate essentially free of blood clotting enzymes and having been treated by heating for a predetermined period of time in the lyophilized form at a temperature between 60°C and 125°C, characterized by said human Factor VIII having both prior to and after heating an AHF purity of greater than about 300 AHF units/gram of protein, by said composition being heated to render substantially inactive a virus related to Acquired Immune Deficiency Syndrome (AIDS) and said AIDS virus being rendered substantially inactive."

Claim 2 of the first auxiliary request was worded identically as claim 1 with the exception that the virus which was being rendered substantially inactive was a non-A, non-B hepatitis virus (NANB hepatitis virus).

Claim 3 and 4 related to specific embodiments of the compositions of claims 1 and 2.

The second auxiliary request submitted before the Opposition Division on 16 December 1992 differed from the claims of the first auxiliary request in that claim 2 had been deleted.

VI. Opponents 03 and 05 filed a notice of appeal against this decision together with a statement of ground of appeal. Opponent 03 later withdrew its appeal.

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

Rubinstein Abstracts

Abstract No. FC-5	Abstract distributed at the XIV Congress of the World Federation of Hemophilia held in San Jose, Costa Rica, on 3 to 7 July 1981,
Abstract No. FC-6	Abstract distributed at the XIV Congress of the World Federation of Hemophilia held in San Jose, Costa Rica, on 3 to 7 July 1981
Abstract No. F-90	Abstract distributed at the Joint Meeting of the 19th Congress of the International Society of Haematology and the 17th Congress of the International Society of Blood Transfusion held in Budapest on 1 to 7 August 1982
Abstract No. 1051	Rubinstein, Thromb. Haemos., Vol. 46, page 338 (1981)
Abstract No. 1054	Rubinstein, Thromb. Haemos., Vol. 46, page 339 (1981)
Abstract No. 650	Rubinstein, Blood, Vol. 58,

page 185a (1981)

Abstract No. 812 Rubinstein, Blood, Vol. 60, page 221a (November 1982)

Other references

(A) WO-A-82/03871

(B) Hollinger et al., Abstract distributed at the 2nd International Max von Pettenkofer Symposium on Viral Hepatitis held in Munich, RFG, on 19 to 22 October 1982

(C) Rozenberg et al., Fed. Proc., Vol. 23, pages T322 to T325 (1963)

(D) Petricciani et al., The Lancet, pages 890 to 891 (19 October 1985)

(E) EP-A-0 018 561

(G) Dr Mosley's affidavit dated 28 March 1988

(J) Barrowcliffe et al., J. Lab. Clin. Med., pages 429 to 430 (March 1981)

(K) Deposition of Dr Rubinstein before the US District Court of Delaware, Vol. I, pages 12, 75 to 77 and 89 to 90 (11 September 1985)

(L) Reports on AIDS Published in the Morbidity and Mortality Weekly Report, June 1981 through February 1986, edited by the Centers for Disease

Control of Atlanta, Georgia, USA, pages 1 to 35 (1986)

(M) Plasma Products: Use and Management presented by The American Association of Blood Banks, Anaheim, California, USA, page 6 (1982)

VIII. Oral proceedings were held on 18 November 1998, during which the Respondent filed a second and a third auxiliary request. Claim 1 of the second auxiliary request reads as follows:

"1. The use of an AHF enriched composition characterized in heating a human Factor VIII concentrate essentially free of blood clotting enzymes for a predetermined period of time in the lyophilized form at a temperature between 60°C and 125°C, said human Factor VIII having both prior to and after heating an AHF purity of greater than about 300 AHF units/gram of protein, to render substantially inactive a virus related to Acquired Immune Deficiency Syndrome (AIDS) and said AIDS virus being rendered substantially inactive for the manufacture of a medicament agent for the substantially AIDS-safe treatment of bleeding disorders."

Claim 2 of the second auxiliary request is worded identically to claim 1 with the exception that the virus which was being rendered substantially inactive was the NANB hepatitis virus.

Claim 1 of the third auxiliary request reads as follows:

"1. The use of an AHF enriched composition prepared by heating a human Factor VIII concentrate essentially free of blood clotting enzymes for a predetermined period of time in the lyophilized form at a temperature between 60°C and 125°C, said human Factor VIII having both prior to and after heating an AHF purity of greater than about 300 AHF units/gram of protein, to render substantially inactive a virus related to Acquired Immune Deficiency Syndrome (AIDS) and said AIDS virus being rendered substantially inactive for the manufacture of a medicament agent for the substantially AIDS-safe treatment of bleeding disorders and preserves substantially all of the antigenicity of said virus."

IX. The Appellant argued essentially as follows:

Article 53a EPC

- Owing to the expression "said AIDS virus being rendered substantially inactive" in claim 1 and "the titre of the virus is reduced so low that infusion of therapeutic quantities of the product...will significantly delay the onset of the infection in such population" on page 10, lines 37 to 40 of the description, the patent in suit was contrary to the "ordre public" or morality because the claimed compositions was susceptible to produce a lethal infection.

Article 83 EPC

- Claim 1 of the third auxiliary request comprised the feature that the antigenicity of the AIDS

virus should substantially be preserved. However, it was impossible for a skilled person to establish whether the antigenicity of the AIDS virus had been substantially preserved at a selected temperature/time combination.

Article 54 EPC

- Document (E) disclosed a lyophilized hepatitis-free Factor VIII preparation which was undistinguishable from the claimed compositions. The only difference was that inactivation of the viruses occurred in solution rather than by heating the lyophilizate. The latter process, however, achieved no technical difference over heating in solution.

- The Rubinstein Abstracts (FC-5, FC-6, FC-90, 1051, 1054, 650 and 812) reported preliminary studies on dry heating commercial preparations of Factor VIII. Since these preparations had been obtained from plasma of thousands of donors, it was very likely that these Factor VIII concentrates were contaminated by AIDS virus (see document (D)) or NANB-hepatitis virus (see document (B)). Since the conditions (temperature/time) for inactivating these viruses disclosed in the patent were the same as those referred to in the Rubinstein Abstracts, it must be concluded that the latter documents already disclosed lyophilized Factor VIII preparations having all the features recited in the claims of the patent in suit, more so as the skilled person was in a position to analyse the product and to establish whether the viruses

had been killed (see decisions T 449/90, supra, and T 952/92, OJ EPO 1995, 755).

Article 56 EPC

- Before the priority date of the patent in suit it was known that viruses could be inactivated by dry heating (see document (C) for hepatitis virus in a fibrinogen preparation and document (A) for hepatitis B virus and NANB-hepatitis virus in preparations containing other blood clotting factors). Once the skilled person became aware of the Rubinstein's work that no substantial loss of Factor VIII activity occurred with certain temperature/time combinations, there was a high expectation of success that viruses would have been inactivated.

- The patent in suit achieves no new technical effect in comparison with the Rubinstein Abstracts since it did not teach which temperature/time combination kill the viruses.

X. The Respondent (Patentee) argued in writing and during oral proceedings essentially as follows:

Main request and first auxiliary request

Article 54 EPC

- The Rubinstein Abstracts related to five experiments involving Factor VIII, three of which were failures, while the remaining two had merely preliminary and uncertain results. It could not be

deduced from these Rubinstein Abstracts whether the Factor VIII was human Factor VIII or of some other origin, with exception of Abstract FC-5 which mentioned "Koate". However, no description of this material's properties was made. The material might have been "rotten" Factor VIII unsuited for therapeutic use but nevertheless good for carrying out these experiments. Further, none of the Rubinstein Abstracts mentioned NANB-hepatitis or AIDS virus.

- The claimed subject-matter was thus novel because the Rubinstein Abstracts did not make available to the public a Factor VIII composition which comprised, beyond any doubt, substantially inactive NANB-hepatitis or AIDS virus. This latter feature was a distinguishing one since the claimed AHF compositions had to comprise the inactivated viruses.

Article 56 EPC

- At the filing date of the patent in suit nothing was known about the structure (protein content, presence or absence of lipids, type of nucleic acid) or the physical conditions of NANB-hepatitis virus or the agent causing AIDS only presumed to be a virus. Lyophilization was known to stabilize biological material. This meant that lyophilization could very well stabilize the contaminating pathogens. There was thus little expectation of success by the skilled person that these pathogenic contaminants would have been substantially inactivated at the temperature/time

combinations disclosed in the Rubinstein Abstracts.

- The claimed AHF compositions, in addition to providing the therapeutic benefits associated with the clotting factor activity, also achieved an immunizing effect against the viruses (see application as filed, page 19, first paragraph).

Second auxiliary request

Article 54 EPC

- Claims 1 and 2 of the second auxiliary request had the format of a second/further medical use. The Rubinstein Abstracts neither mentioned any NANB-hepatitis or AIDS viruses nor said anything as to whether these viruses had been substantially inactivated by the temperature/time combinations selected therein. Therefore, none of the Rubinstein Abstracts made available to the public the knowledge that those dry heated Factor VIII preparations could actually be used for the AIDS-safe or NANB-safe treatment of bleeding disorders.

Article 56 EPC

- Since nothing was known about the structure of NANB-hepatitis virus or the agent causing AIDS only presumed to be a virus, there was little expectation of success by the skilled person that the dry heated Factor VIII preparations disclosed in the Rubinstein Abstracts could actually be used for the AIDS-safe or NANB-safe treatment of

bleeding disorders.

- The claimed medical use also achieved an immunizing effect against the viruses (see application as filed, page 19, first paragraph).

Third auxiliary request

Article 54 EPC

- Claim 1 of the third auxiliary request further comprised the feature that the antigenicity of the AIDS virus should substantially be preserved. The Rubinstein Abstracts did not mention any AIDS virus nor said anything as to whether this virus had been substantially inactivated by the temperature/time combinations selected therein, let alone that the antigenicity of the AIDS virus had been substantially preserved.

Article 56 EPC

- In contrast to more drastic virus inactivation methods, such as covalent reactions with chemical substances, high energy irradiation or excessive heating, the mild dry heating process of the invention preserved all of the antigenicity of the infectious microbes, i.e the epitopic sites on the organism were not irreversibly denatured (see application as filed, page 23, lines 21 to 26). Thus the claimed medical use also achieved an immunizing effect against the AIDS virus.

XI. The Appellant did not dispute that the claims of all

requests satisfied the requirements of Article 123(2) and (3) EPC. The Parties agreed that for the purposes of Article 54(2) and (3) EPC, it was the date of filing of the European patent application (11 May 1983) which was relevant for the subject-matter of the claims of all requests.

XII. The Appellant requested that the decision under appeal be set aside and that the European patent No. 0 094 611 be revoked.

The Respondent (Patentee) requested that the appeal be dismissed (main request), auxiliarily that the decision under appeal be set aside and the patent be maintained on the basis of either of the following requests:

(a) claims 1 to 3 of the "second auxiliary request" filed on 16 December 1992 (now first auxiliary request), or

(b) claims 1 to 4 filed in the oral proceedings as the second auxiliary request, or

(c) claims 1 to 3 filed in the oral proceedings as the third auxiliary request,

and a description to be adapted thereto.

Reasons for the Decision

Right to priority (Article 88(3) EPC)

1. During the oral proceedings, the Parties agreed that for the purposes of Article 54(2) and (3) EPC, it was the date of filing of the European patent application (11 May 1983) which was relevant for the subject-matter of the claims of all requests because the priority (13 May 1982) could not validly be claimed. The Board agrees as well. In fact, claim 1 of all requests comprises a reference to "a virus related to Acquired Immune Deficiency Syndrome (AIDS)" which is neither cited expressis verbis in the priority document US 377863 nor is implicitly derivable therefrom.

In this context the Board notes that previously Board 3.3.2 (see decision T 449/90 and Section IV, supra), when dealing with the issue of sufficiency of disclosure, found that the feature of inactivation of the NANB-hepatitis or AIDS virus upon dry heating had to be testable by the skilled person in order that the requirements of Article 83 be fulfilled. It was acknowledged that before the filing date of the patent in suit, there were no techniques to cultivate NANB-hepatitis or AIDS virus so that consequently no means for a direct detection of theses viruses in a living entity or a cell culture or indirect tracing by measuring the antibodies possibly raised against these viruses was at hand. But there are passages in the application as filed on page 22, lines 24 to 37 and on page 23, lines 1 to 5 incorporating a reference to a PCT International Application WO 82/03871 (document (A)), relating to a method for testing virus inactivation in dry heated blood clotting factors preparations based on the use of thermally highly stable viruses (eg the sindbis virus) as virus inactivation indicators. This technical information was

considered by that Board 3.3.2 to be sufficient for the skilled person to evaluate whether NANB-hepatitis or AIDS virus had been substantially inactivated by the heat treatment and thus the requirements of Article 83 EPC were found to be fulfilled. However, the mentioned passages in the application as filed, essential for the patent application to meet the requirements of Article 83 EPC has no counterpart in the priority document US 377863, which is thus not enabling for the claimed subject matter.

Article 123(2) and (3) EPC

2. The features "at a temperature between 60°C and 125°C" and "said human Factor VIII having both prior to and after heating an AHF purity of greater than about 300 AHF units/gram of protein" in claims 1 and 2 of the main request, in claim 1 of the first auxiliary request, in claims 1 and 2 of the second auxiliary request and in claim 1 of the third auxiliary request (were decided in T 449/90, supra, point 2). Therefore the issue of conformity with the requirements of Article 123(2) EPC of these features is res judicata. This also applies to the wording "said composition being heated to render substantially inactive a virus related to Acquired Immune Deficiency Syndrome (AIDS) and said AIDS virus being rendered substantially inactive" in claim 1 of all requests.

The feature "non-A, non-B hepatitis virus" in claim 2 of the main request is equivalent to "NANB-hepatitis virus" in claim 2 of the second auxiliary request and finds a basis on page 18, lines 30 to 31 and in claim 44 of the application as filed.

The claims of the second and third auxiliary requests have the format of a second/further medical use, i.e the dry-heated AHF preparation should be used for the manufacture of a medicament for the substantially AIDS-safe or NANB-hepatitis-safe treatment of bleeding disorders. This medical use can be derived from page 22, lines 1 to 3 in combination with page 18, line 31 and page 19, line 32 to 35 of the application as filed.

Also the expression "and preserves substantially all of the antigenicity of said virus" in claim 1 of the third auxiliary request finds a formal basis on page 23, lines 21 to 24 of the application as filed.

All the features listed above were either already present in the granted claims or are restrictive in nature. The requirements of Article 123(2) and (3) EPC are thus fulfilled.

Objection under Article 53a EPC

3. The Appellant submitted that the patent in suit was contrary to the "ordre public" or morality because the claimed Factor VIII compositions were susceptible to produce a lethal infection. However, this objection under Article 53a EPC is a new ground of opposition which could only be introduced at such a late stage into the appeal proceedings with the approval of the Patentee (see decision G 10/91, OJ EPO 1993, 420), which it has not. While it is true, as argued by the Appellant, that Opponent 01 (see submission of 24 February 1998, page 10) already argued that the claimed compositions could still contain not fully

inactivated NANB hepatitis and AIDS viruses, this objection was raised under Article 57 EPC in the sense that such compositions lacked industrial application. The objection under Article 53a EPC is inadmissible.

Main request and first auxiliary request

Novelty (Article 54 EPC) of claims 1 and 2 of the main request and of claim 1 of the first auxiliary request

4. These claims are all directed (see Section V supra) to AHF enriched compositions having been heated in the lyophilized form to render substantially inactive a non-A, non-B hepatitis virus (NANB hepatitis virus) or a virus related to Acquired Immune Deficiency Syndrome (AIDS). A product as such is not explicitly disclosed by any prior art document. However, it is well established in the case law of the Boards of Appeal, following from decisions T 12/81 (OJ EPO 1982, 296) and T 181/82 (OJ EPO 1982, 401), that carrying out certain known processes on certain known starting materials must inevitably lead to the same certain result. This Board agrees to this position.

The so-called Rubinstein Abstracts (FC-5, FC-6, FC-90, 1051, 1054, 650 and 812) report preliminary studies on dry heating Factor VIII concentrates. When applying the rationale emerging from the above cited decisions, it has thus to be evaluated whether the process and the starting material recited in claims 1 and 2 of the main request and in claim 1 of the first auxiliary request (wording of the claims, see Section V supra) are the same as those disclosed in the Rubinstein Abstracts.

5. As regards the processes, the Board notes that the dry heating process recited in the claims at issue occurs under the same conditions (temperature/time) as the dry heating process referred to in the Rubinstein Abstracts. This is shown by a comparison between the wording in these claims "heating ...at a temperature between 60°C and 125°C for a predetermined period of time" with the temperature/time conditions referred to in the Rubinstein Abstracts (Abstracts No. FC-5, 650 and 1054: 60°C/10 hrs; Abstract No. FC-6: 62°C-64°C/16 hrs, 74°C/13 hrs and 78°C/15 hrs; Abstract No. 1051: 62°C-64°C/16 hrs and 100°C/30 min; Abstract No. F-90: 80°C/10 hrs, 78°C/21 hrs and 100°C/30 min; Abstract No. 812: 75°C/18.5 hrs and 78°C/19 min 20 sec).

6. Turning now to the starting material, the "AHF enriched composition" (the acronym "AHF" means antihemophilic factor, another name for Factor VIII) to be heated in the lyophilized form according to these claims has to be compared with the "Factor VIII concentrate" being dry heated according to the Rubinstein Abstracts in order to evaluate whether there are or not technical differences between these two products.

7. The composition recited in these claims is an "AHF enriched composition, i.e. a Factor VIII concentrate essentially free of blood clotting enzymes and having a purity of greater than about 300 AHF units/gram of protein". It is thus a commercial Factor VIII concentrate as transpires from page 3, lines 11 to 12 ("Paired samples ...were received from several manufacturers") and from the footnotes to Tables I and II of the patent in suit. As regards the presence of viruses in these commercial Factor VIII concentrates,

it is stated in Section 12 on page 7 of Dr Mosley's affidavit, a Respondent's expert (see document (G)), that it was very likely that at least some of the Factor VIII concentrates identified by manufacturer and lot number in the patent in suit were contaminated with one or both of the virus types referred to in the independent claims, namely the NANB-hepatitis virus and/or the AIDS virus. The Board agrees with this statement by Dr Mosley. In fact, commercial Factor VIII preparations were made from plasma from thousands of donors and thus the possibility can not be excluded that some preparations were contaminated with viruses. The Respondent maintains that the claimed AHF compositions **must** comprise the inactivated viruses. Yet this Respondent's interpretation of the claims would of necessity imply as an additional step the deliberate addition of NANB-hepatitis and/or AIDS virus to the AHF preparations before the dry heating step. The Board cannot accept that this additional measure has actually to be taken if one follows the teaching of the patent in suit. Thus, in conclusion, the starting product referred to in the claims at issue is a lyophilized AHF concentrate essentially free of blood clotting enzymes and having an AHF purity of greater than about 300 AHF units/gram of protein, **possibly** contaminated by the NANB-hepatitis virus and/or the AIDS virus.

8. The Factor VIII compositions dry heated by Dr Rubinstein in his series of tests thereafter published as the Rubinstein Abstracts were apparently lyophilized commercial Factor VIII concentrates. This is evident from Abstract FC-5, which cites "Koate" (the brand name for Factor VIII preparation sold by Cutter Laboratories). According to document (J) (see Table I),

Koate is a high purity concentrate, which exhibits a specific activity of 1,020 U/gram of protein. In fact, it transpires from this Table I that high purity Factor VIII preparations from any manufacturer had a specific activity higher than 300 U/mg of protein and were free of other blood clotting enzymes. Dr Rubinstein himself submitted (see document (K), page 62, lines 16 to 18) that he used for his investigations lyophilized Factor VIII concentrates from the pharmacy of Cedars-Sinai. Thus, the Board is not convinced of the submission by the Respondent that the starting material used by Dr Rubinstein was "rotten" material. It also transpires from the Rubinstein Abstracts that the Factor VIII preparations were commercial preparations susceptible of being infected by viruses. This is because Rubinstein Abstracts No. 1051, FC-6, 650 and 812 contain the final statement that chimpanzee studies were planned to determine whether the heating had significantly inactivated the viruses. The Board judges this statement as a further evidence that the Factor VIII compositions dry heated by Dr Rubinstein were commercial Factor VIII preparations made from pools from thousands of donors, which were thus susceptible of containing viruses. As to the viruses **possibly** present in Dr Rubinstein's starting products, one was the NANB-hepatitis virus. The patent in suit indeed confirms (see page 2, lines 7 to 12) that any commercial Factor VIII concentrate was potentially contaminated with the NANB-hepatitis virus. This is in line with the statement on page 6 of document (M): "Plasma derivatives, made from large plasma pools, must be assumed to be contaminated with hepatitis viruses (B or "non-A, non-B")". As regards contamination with the AIDS virus, document (D) states: "Data available from

over half a million samples tested in the United States up to April/May, 1985, suggest that about 0.2% of random blood and plasma donors are positive (repeatedly reactive) for antibody to LAV/HTLV..."). Document (L) (see pages 14 to 15 and 24 to 25) even shows that transmission of the AIDS virus to patients treated with injections of commercial Factor VIII concentrates occurred as early as 1981 and 1982, i.e., before Rubinstein Abstract No. F-90 was distributed at a Congress held in Budapest on 1 to 7 August 1982, and Abstract 812 was handed over at a congress held in Washington D.C. on 4 to 7 December 1982. These Abstracts represent prior art according to Article 54(2) EPC (see point 1 supra).

9. In view of the above findings, the Board concludes that, as in the case of the starting material referred to in claims 1 and 2 of the main request and in claim 1 of the first auxiliary request (see point 4 supra), the starting material dealt with in the Rubinstein Abstracts were likewise lyophilized commercial Factor VIII concentrates essentially free of blood clotting enzymes and having an AHF purity of greater than about 300 AHF units/gram of protein, **possibly** contaminated by the NANB-hepatitis virus and/or the AIDS virus. Thus, the inevitable result of carrying out the known process on known starting material must lead to the same end product. Claims 1 and 2 of the main request and claim 1 of the first auxiliary request lack novelty. These requests have thus to be refused.

Second auxiliary request

Novelty (Article 54 EPC)

10. Claims 1 and 2 of the second auxiliary request have the format of a second/further medical use, i.e the dry-heated AHF preparations are to be used for the manufacture of a medicament for the substantially AIDS-safe (claim 1) or NANB-hepatitis-safe (claim 2) treatment of bleeding disorders. The Board agrees to the Respondent's position that none of the Rubinstein Abstracts made available to the public that those dry heated Factor VIII preparations could actually be used for the AIDS-safe or NANB-safe treatment of bleeding disorders. These claims and dependent claims 3 and 4 of the second auxiliary request are thus novel.

Inventive step

Closest prior art

11. The Parties agreed that for the purpose of Article 56 EPC, the closest prior art is represented by the Rubinstein Abstracts, in particular Abstracts FC-5 and 812, and the Board agrees as well. These Abstracts relate to Dr Rubinstein's investigations on the extent of retention of biological activity of lyophilized commercial Factor VIII concentrates upon heating at various temperature/time combinations. Nothing is said in these Abstracts as to whether these selected temperature/time combinations are capable or not to kill contaminating viruses.

Problem to be solved

12. The patent in suit also does not report any measure of the viral infectivity of the heat treated Factor VIII concentrates. In fact, if one attempts to achieve the goal recited in the claims, namely to use the dry heated commercial Factor VIII concentrate for the manufacture of a medicament for the substantially AIDS-safe (claim 1) or NANB-hepatitis-safe (claim 2) treatment of bleeding disorders, the disclosure provided by the patent in suit leaves the skilled person with the **same** uncertainty and need for further investigation as was left the person reading the Rubinstein Abstracts. Thus, the conclusion cannot be drawn that the problem to be solved by the patent in suit compared with the Rubinstein Abstracts was to provide evidence that the selected temperature/time combinations which did not substantially affect the biological activity of Factor VIII were also effective in inactivating the NANB-hepatitis or AIDS viruses.

13. Rather, Dr Mosley, a Respondent's expert states (see document (G), page 8, Section 13) that: "The EPO patent itself does not actually measure the viral infectivity of heat treated Factor VIII concentrates identified in, e.g., Tables I and II of the Patent, but does provide a discussion of the manner in which effects of heating virus-contaminated Factor VIII concentrate in the lyophilized state may be "followed" (EPO Patent, page 10, lines 24 to 31)". The Board agrees. In fact, the only technical teaching beyond what was already disclosed in the Rubinstein Abstracts, which the Board is able to identify in the patent in suit is that the latter provides the means for "following" i.e.

monitoring how inactivation of NANB-hepatitis or AIDS viruses proceeds at the selected temperature/time combinations and for testing whether these viruses contaminating the Factor VIII concentrates are substantially inactivated (see patent in suit, page 10, lines 24 to 31), in order to render possible the use stated in the claims. In view of this finding, the Board considers that the problem the patent in suit purports to solve, starting from the Rubinstein Abstracts as the closest prior art, consists in providing the means for monitoring how inactivation of NANB-hepatitis or AIDS viruses proceeds and for testing whether these viruses contaminating the Factor VIII concentrates are substantially inactivated, so as to render possible the use stated in the claims. These means are based on the use of thermally highly stable viruses (e.g., the sindbis virus) as virus inactivation indicators, as disclosed by document (A) (see point 1 supra). Insofar as the problem to be solved by patent is viewed in this way, the Board is satisfied that the patent in suit provides the technical information needed for solving this problem since the means and methods for testing the AHF purity and clotting activity are disclosed in detail on page 3, lines 10 to 45 of the patent specification, whereas a method for monitoring how inactivation of the virus proceeds and for testing whether these viruses contaminating the Factor VIII concentrates are substantially inactivated, be it NANB-hepatitis or AIDS virus, is disclosed on page 10, lines 24 to 31. However, like the Rubinstein Abstracts, the patent in suit leaves the skilled person with the burden of still finding out temperature/time combinations at which the viruses are "substantially inactivated" (see point 10 supra).

14. The relevant question in respect of inventive step is whether the solution to the above problem proposed by the patent in suit is obvious or not in the light of the prior art. As already stated in point 1 supra, before the filing date of the patent in suit, there were no techniques to cultivate NANB-hepatitis or AIDS virus so that consequently no means for a direct detection of theses viruses in a living entity or a cell culture or indirect tracing by measuring the antibodies possibly raised against these viruses was at hand. However, document (A) discloses a method for testing virus inactivation in dry heated blood clotting factors preparations based on the use of thermally highly stable viruses (e.g., the sindbis virus) as virus inactivation indicators. In the Board's judgement, adopting this technique for overcoming the problem the patent in suit purports to solve departing from the Rubinstein Abstracts as closest prior art and to arrive at the claimed subject matter, was **the** obvious step to be taken.

15. The Respondent argued that there was little expectation of success by the skilled person that NANB-hepatitis virus or the agent causing AIDS only presumed to be a virus would have been substantially inactivated at the temperature/time combinations disclosed in the Rubinstein Abstracts, bearing in mind that at the filing date of the patent in suit nothing was known about the structure of these pathogens. The Board, however, observes that the technique disclosed in document (A) consisting in using thermally highly stable viruses (eg the sindbis virus) as virus inactivation indicators is a very powerful tool. This transpires from e.g., Example VI of document (A) which

illustrates the use of the thermally highly stable virus T4 bacteriophage as a virus inactivation indicator. It is stated on page 30, lines 16 to 20 that once the T4 phage was found to have been inactivated by heat treatment, the conclusion could be drawn that the heat treatment was successful at inactivating **any endogenous viruses** (emphasis added). In conclusion, the above Respondent's line of argument is not convincing in view of this passage of document (A) which suggests that the skilled person considered it very unlikely that some pathogen present in the lyophilized blood clotting factor preparation might have been thermally more resistant than the thermally highly stable virus used as virus inactivation indicator. Consequently, claims 1 and 2 of the second auxiliary request lack an inventive step (Article 56 EPC). This request has thus also to be refused.

Third auxiliary request

Article 83 EPC

16. Claim 1 of the third auxiliary request differs from claim 1 of the second auxiliary request in that it further comprises the feature that the antigenicity of the AIDS virus should substantially be preserved. As emphasized in points 1 and 12 supra, before the filing date of the patent in suit, there were no techniques to cultivate the AIDS virus and no means for a direct detection of this virus in a living entity or a cell culture or indirect tracing by measuring the antibodies possibly raised against this virus was at hand. Therefore, it was also impossible for a skilled person

to establish whether the antigenicity of the AIDS virus had been substantially preserved at a selected temperature/time combination. While the technique referred to in the patent relying on the thermally highly stable virus as virus inactivation indicator was a powerful tool for evaluating substantial inactivation of the AIDS virus, this expedient was, for obvious reasons, unsuited to establishing the substantial preservation or not of the antigenicity of the AIDS virus. Consequently, claim 1 of the third auxiliary request does not meet the requirements of Article 83 EPC. This request has thus also to be refused. In view of this negative finding in connection with sufficiency of disclosure (Article 83 EPC), it superfluous to evaluate whether or not the claims of the third auxiliary request fulfil the requirements of Articles 54 and 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. European patent No. 0 094 611 is revoked.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey