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Datasheet for the decision of 14 February 2006

Case Number: T 0562/04 - 3.3.04

Application Number: 93902233.1

Publication Number: 0625161

IPC: C07K 1/18

Language of the proceedings: EN

Title of invention:
Process for recovering a high-purity virus-inactivated factor VIII/von Willebrand factor complex by anion exchanger chromatography

Patentee:
Octapharma AG

Opponent:
Baxter Healthcare S.A.

Headword:
Factor VIII/von Willebrand factor complex/OCTAPHARMA

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 87(1), 88, 89, 111(1), 113(1), 114(2), 123(2)(3)

Keyword:
"Admissibility of late-filed documents - (yes)"
"Remittal - (no)"
"Main request - novelty (no)"
"Auxiliary request - added subject-matter, extension of scope of protection (no), clarity, novelty, sufficiency of disclosure, inventive step (yes)"

Decisions cited:
G 0002/98, T 0005/90, T 0019/90, T 1019/92, T 0649/97

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0562/04 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 14 February 2006

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 25 March 2004 rejecting the opposition filed against European patent No. 0625161 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: R. Moufang
Members: G. Alt
R. Gramaglia

Summary of Facts and Submissions

I. The appeal was lodged by the opponent (appellant) against the decision of the opposition division to reject the opposition against European patent No. 0 625 161 under Article 102(2) EPC.

II. The application from which the patent in suit derives (European application No. 93 902 233.1) was filed as international application No. PCT/EP 93/00114 claiming the priority of document DE 4204694 of 1 February 1992. The application was published under the international publication number WO93/15105. The international application as filed contained independent claim 1 directed to a process for recovering a highly pure virus-inactivated factor VIII from blood plasma or cryoprecipitate by means of anion exchanger chromatography and seven further claims dependent on it.

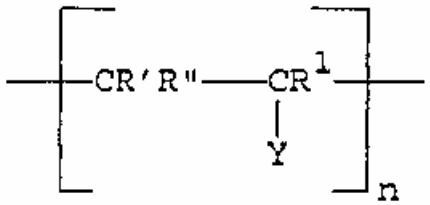
Claim 6 read:

"6. A process for recovering a highly pure virus-inactivated factor VIII from blood plasma or cryoprecipitate by means of anion exchanger chromatography using an anion exchanger material according to at least one of claims 1 through 5, wherein the purification of factor VIII is effected by washing and eluting with buffers having subsequently increasing ionic strengths, characterized in that the ionic strength of the buffer is adjusted by means of quaternary ammonium salts having at least one hydrocarbyl chain having from 1 to 6 carbon atoms and bearing a hydrophilic substituent alone or in combination with common salt."

III. The patent had been granted on the basis of claims 1 to 6.

Claims 1 and 4 as granted read:

"1. A process for recovering a highly pure virus-inactivated factor VIII/von Willebrand factor complex from cryoprecipitate by means of anion exchanger chromatography, characterized in that there is used, as the anion exchanger material, a separating material based on carriers containing hydroxyl groups, the surfaces of which carriers have been coated with covalently bonded polymers, said polymers containing repeating units which are same or different and are represented by the formula I



I,

wherein

R^1 represents H or CH_3

Y represents

$-CH_2-NH_2$ or $-CH_2NR^2R^3$,

R' and R'' each represent H or CH_3,

X represents $-NR^2R^3$,

R^2 and R^3 each represent an alkyl, phenyl, phenylalkyl or alkylphenyl group having up to 10 carbon atoms in the alkyl moiety, which groups are mono- or poly-substituted with amino, mono— or dialkylamino, trialkylammonium, carboxyl and may be mono- or poly-substituted with alkoxy, cyano, sulfonic acid, acetoxy or acetamino moieties,

a cyclic or bicyclic moiety having from 5 to 10 carbon atoms, wherein one or more CH— or CH_2—groups have been replaced by N or NH, N or NH and S, or N or NH and O,

one of R^2 and R^3 may also represent H, while R^2 and R^3 have been adjusted to each other so that both moieties either contain basic groups or one of the two moieties is neutral, and

n represents from 2 to 100."

"4. The process according to claim 1 for recovering a highly pure virus-inactivated factor VIII/von Willebrand factor complex from cryoprecipitate by means of anion exchanger chromatography using an anion exchanger material according to at least one of claims 1 through 3, wherein the purification of factor VIII is effected by washing and eluting with buffers having subsequently increasing ionic strengths, characterized in that the ionic strength of the buffer is adjusted by means of quaternary ammonium salts having at least one hydrocarbyl chain having from 1 to 6 carbon atoms and bearing a hydrophilic substituent alone or in combination with common salt."

IV. The patent had been opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), under Article 100(b) EPC and under Article 100(c) EPC on the ground that the subject-matter of the patent extended beyond the content of the application as filed (Article 123(2) EPC).

V. With the statement setting out the grounds of appeal the appellant submitted document EP 0 567 448 (hereinafter document D9) claiming the priority date of 24 April 1992 of document AT 849/92 and the document "Biochromatographie Trennung von Biopolymeren", a product specification sheet of Merck, Darmstadt, Germany (hereinafter document D10).

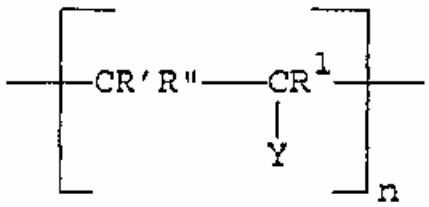
VI. With the submission dated 12 January 2006 the respondent submitted auxiliary requests I to IV.

VII. With the submission dated 20 January 2006 the appellant filed Annex 1 comprising a set of experiments aimed at demonstrating that the subject-matter of the claim of the main request was based on technical effects which were not achievable over the whole area claimed.

VIII. At the oral proceedings held on 14 February 2006 auxiliary request I was filed corresponding to auxiliary request II filed in writing, claim 1 of this request corresponding to a combination of claims 1 and 4 as granted and reading as follows:

"1. A process for recovering a highly pure virus-inactivated factor VIII/von Willebrand factor complex from cryoprecipitate by means of anion exchanger

chromatography, characterized in that there is used, as the anion exchanger material, a separating material based on carriers containing hydroxyl groups, the surfaces of which carriers have been coated with covalently bonded polymers, said polymers containing repeating units which are same or different and are represented by the formula I



I,

wherein

R^1 represents H or CH_3

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X represents $-NR^2R^3$,

R^2 and R^3 each represent an alkyl, phenyl, phenylalkyl or alkylphenyl group having up to 10 carbon atoms in the alkyl moiety, which groups are mono- or poly-substituted with amino, mono— or dialkylamino, trialkylammonium, carboxyl and may be mono- or poly-substituted with alkoxy, cyano, sulfonic acid, acetoxy or acetamino moieties,

a cyclic or bicyclic moiety having from 5 to 10 carbon atoms, wherein one or more CH— or CH_2—groups have been replaced by N or NH, N or NH and S, or N or NH and O,

one of R^2 and R^3 may also represent H, while R^2 and R^3 have been adjusted to each other so that both moieties either contain basic groups or one of the two moieties is neutral, and

n represents from 2 to 100,

and wherein the purification of factor VIII is effected by washing and eluting with buffers having subsequently increasing ionic strengths, the ionic strength of the buffer is adjusted by means of quaternary ammonium salts having at least one hydrocarbyl chain having from 1 to 6 carbon atoms and bearing a hydrophilic substituent alone or in combination with common salt."

The request contained four further claims dependent on claim 1.

IX. The following documents are cited in this decision:

D1: EP-A-0 416 983

D2: EP-A-0 337 144

D3: EP-A-0 359 593

D4: EP-A-0 343 275

D7: Hearn, M.T. W. et al., Journal of Chromatography, vol. 548, (1991), pages 117-126

D8: Haemostasis and Thrombosis, Bloom, A.L. and Thomas, D.P. (Editors), Churchill Livingstone (second edition), 1987, pages 131-147

D9: EP-A-0 567 448

D10: "Biochromatographie Trennung von Biopolymeren"; product specification sheet of Merck, Darmstadt, Germany; pages 1 to 22, published October 1989

Annex 1 filed with the appellant's submission dated 20 January 2006

X. Requests

The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 625 161 be revoked.

The respondent (patentee) requested that the appeal be dismissed and that the patent be maintained in unamended form or, in the alternative, that the decision under appeal be set aside and the patent be maintained in amended form on the basis of claims 1 to 5 of auxiliary request I filed in the oral proceedings.

The respondent (patentee) further requested that documents D9 and D10 not be admitted into the proceedings or, in the alternative, that the case be remitted for further prosecution to the department of first instance in order to consider the patentability of the subject-matter of the claims as granted in view of document D9.

XI. The submissions made by the appellant as far as they are relevant to the present decision may be summarised as follows:

Admissibility into the proceedings of documents D9 and D10

Document D9 was prima facie relevant because it disclosed the process claimed in the claims of the main request. Document D10 was relevant because it disclosed the chromatographic material used in the respective process of document D9.

The filing of document D9 with the statement setting out the grounds for appeal was not an abuse of the procedure. The document could not have been filed earlier because the non-validity of the date of priority of the patent in suit only came to light in the course of the search for further arguments after the opponent's unsuccessful opposition against the patent in suit.

Remittal

Documents D9 and D10 were filed with the statement of the grounds of appeal, i.e. very early in the appeal proceedings. Thus, the respondent and the board had sufficient time for their consideration.

Moreover, the priority situation and the disclosure content of document D9 were clear. Therefore, the issue was not complex. Accordingly, the case should not be remitted to the opposition division.

Main request - claims as granted

Article 123(2) EPC

There was no explicit disclosure of a highly pure virus-inactivated factor VIII/von Willebrand factor complex in the application documents as originally filed. Neither was there an implicit disclosure since, having regard to the fact that factor VIII and von Willebrand factor had greatly differing molecular weights, a skilled person envisaging the process disclosed in the patent in suit, would consider it as unlikely that both factors would elute simultaneously from an anion exchange column. Support for this view came from the disclosure of document D3, showing that during purification of factor VIII and von Willebrand factor using anion exchange chromatography and buffers comparable to the ones used in the patent in suit, most of the von Willebrand factor was eluted first and then, by increasing the ionic strength of the buffer, factor VIII was eluted in the presence of only small quantities of von Willebrand factor. For that reason the statement on page 14 of the application as originally filed describing that it would be advantageous not to remove the von Willebrand factor from factor VIII would not be understood by the skilled person as disclosing the recovery of a complex of the two factors. Likewise, the Table on page 20 of the application as filed could not change the skilled person's estimation because he/she would read the Table as merely listing the overall workup product of a purification of a cryoprecipitate solution.

Since the recovery of a factor VIII/von Willebrand factor complex was not disclosed, the recovery of a "highly pure factor VIII/von Willebrand factor complex" was not disclosed either.

Novelty

Validity of the priority of the patent in suit

The priority document pertaining to the patent in suit literally disclosed neither the term "von Willebrand factor" nor the term "complex".

The decision of the opposition division to consider the replacement of the term "factor VIII" by the term "factor VIII/von Willebrand factor complex" as acceptable under Article 123(2) EPC essentially relied on the disclosure on page 14 of the application as filed. However, this passage and also the Table on page 20 were absent in the priority document. Thus, there was no implicit disclosure of the term in the priority document.

Moreover, it was known from document D8 that factor VIII and von Willebrand factor were two distinct molecular entities forming a third molecular entity, i.e. a complex of both. Thus, a document explicitly referring to factor VIII could not be construed as implicitly relating to a factor VIII/von Willebrand factor complex.

For these reasons the priority was not valid for the subject-matter of the claims.

Document D9

Example 2 of document D9 disclosed a process comprising all the process steps stated in claim 1. The final product of the process of Example 2 was said to be a factor VIII-comprising fraction ("Faktor VIII-hältige Fraktion").

In column 3, lines 7 to 11, it was stated that the process disclosed in document D9 could lead to three alternative products, i.e. Factor VIII, von Willebrand factor or a factor VIII/von Willebrand factor complex wherein the first two products could be obtained from the complex by a dissociation step. No such step was apparent from Example 2. Therefore, the final product of the process was a complex. Hence, taking into account its whole disclosure content, document D9 destroyed the novelty of claim 1.

Auxiliary request I

Article 83 EPC

It was neither defined in the patent in suit what degree of purity was contemplated by the definition "highly pure", nor was the meaning of the definition evident to the skilled person. Accordingly, the process was not disclosed sufficiently for it to be carried out by a skilled person who did not know which product he/she was aiming to obtain.

Inventive step

The closest prior art document was represented by either document D3 or document D1.

The subject-matter of claim 1 differed from the disclosure of document D3 in that a different chromatographic material was used, namely a so-called tentacle-based ion exchanger and in that a quaternary ammonium salt having at least one hydrocarbyl chain having from 1 to 6 carbon atoms and bearing a hydrophilic substituent was used alone or in combination with common salt to adjust the ionic strength of washing and elution buffers.

The problem to be solved was the provision of a further process for the preparation of a factor VIII/von Willebrand factor complex.

It was questionable whether the problem could be considered as solved by the patent in suit, because none of the examples reflected the now claimed process.

If it was acknowledged that the problem was solved, the subject-matter had to be considered as obvious.

The use of quaternary ammonium salt was a routine measure. The replacement of the ion exchange material disclosed in document D3 by the tentacle-type material was obvious, because the latter was known from document D2 and was also commercially available. Moreover, there was no suggestion in the prior art that the complex could not be successfully isolated with that material.

On the contrary, it was reported in column 3 of document D1 that the tentacle-based resin differed from the "normal" resin only with respect to the capacity of the gel.

An inventive step also had to be denied if document D1 was taken as the closest prior art document because cryoprecipitate was a well-known starting material for the isolation of factor VIII, von Willebrand factor or the complex of both.

Moreover, the subject-matter of claim 1 was not inventive because the intended effect of the process, namely the isolation of a factor VIII/von Willebrand factor complex was not achieved by all process alternatives falling under the terms of the claim as demonstrated by experiments filed with Annex 1.

XII. The submissions made by the respondent as far as they are relevant to the present decision may be summarised as follows:

Admissibility into the proceedings of documents D9 and D10

Document D9 could only become relevant under Article 54(3) EPC provided the priority of the patent in suit was not valid, while the priority of document D9 itself was.

Document D9 could only be understood with the help of the further document D10.

The example cited against the novelty of claim 1, Example 2, did not even mention von Willebrand factor.

For these reasons the documents could not be considered prima facie relevant and should not be admitted.

Furthermore, in the present case, the late filing amounted to an abuse of procedure. Baxter AG was the legal successor of Immuno AG, which had been the proprietor of the patent derived from document D9. Therefore, the appellant knew of the existence of document D9 and could have filed it earlier. Nevertheless, it was submitted late without an adequate excuse.

Remittal

The question of whether or not document D9 destroyed the novelty was difficult to answer because it hinged, firstly, on the correct evaluation of the priority situation and, secondly, it necessitated an interpretation of the disclosure content of document D9. Document D9 might be considered as disclosing all elements of the claimed process, but certainly not in combination.

These complex issues had to be considered by two instances.

Main request - claims as granted

Article 123(2) EPC

The application documents as originally filed provided a clear and unambiguous basis for a process for recovering a highly pure virus-inactivated factor

VIII/von Willebrand factor complex because it was stated on page 14 that it was "advantageous that in the process according to the invention the so-called von Willebrand factor is not removed, but remains in the factor VIII fractions". Moreover, the Table on page 20 disclosing the results of the process according to the patent in suit mentioned factor VIII and von Willebrand factor. Since it was known that factor VIII and von Willebrand factor formed a complex, the disclosure of the non-removal of one from the other (page 14) and of the presence of both (Table) was the disclosure of a complex.

Novelty

Validity of the priority of the patent in suit

According to the opinion given by the Enlarged Board of Appeal in G 2/98 it was essential that all technical features defining the invention be present in the priority document. This was the case here because all the claimed process steps were disclosed in the priority document. The only difference was that the stated purpose of the process was different, i.e. it was the preparation of factor VIII according to the priority document and of a factor VIII/von Willebrand factor complex according to the claims of the main request. However, at the priority date the skilled person knew that factor VIII existed as a complex with von Willebrand factor. Hence, he/she would understand a claim covering a process for the preparation of factor VIII as being implicitly directed to the preparation of factor VIII/von Willebrand factor complex.

Document D9

Document D9 disclosed three alternative end-products for its process. Since the exact nature of the end-product of the process of Example 2 was stated in terms of "factor VIII-comprising fraction", it was not known which of the two alternative products, i.e. factor VIII or factor VIII/von Willebrand factor complex was prepared. Hence, even when taking into account the whole disclosure content of document D9 and although the process steps of Example 2 may correspond to those of claim 1, a process for preparation of the complex was not clearly and unambiguously disclosed by that example.

Auxiliary request I

Article 83 EPC

The argument that the invention was not sufficiently disclosed because the term "highly pure" was ambiguous, was a disguised argument of lack of clarity. However, the term was not open to an objection under Article 84 EPC because it was not the result of an amendment, see claims 1 and 4 as granted.

Inventive step

The closest prior art document was document D1 because it disclosed a process for the preparation of a factor VIII/von Willebrand factor complex.

The problem to be solved was the provision of a factor VIII/von Willebrand factor complex with especially high activity.

Document D1 used blood plasma as a starting material and emphasised that cryoprecipitate should be avoided. The use of exactly that material in the process according to the claims can only be regarded as non-obvious.

The use of the tentacle-type ion exchange material was not obvious because the fact that it was commercially available did not necessarily mean that a skilled person would have used it.

The experiments in Annex 1 did not reflect the conditions prescribed in claim 1 of the auxiliary request and were therefore not suited to support the appellant's argument that the intended effect was not achieved by the process over the whole area claimed.

Reasons for the Decision

Admissibility into the proceedings of documents D9 and D10

1. Pursuant to Article 114(2) EPC, facts or evidence which are not submitted in due time by the parties concerned may be disregarded. Certain criteria were developed in the case law of the boards of appeal regarding the exercise of the discretion, the main criterion being the relevance of the late-filed material (c.f. Case Law of the Boards of Appeal of the European Patent Office, Chapter VI, F.3, 3.1).

As follows from points 23 to 29 below, the board considers document D9 as highly relevant.

2. According to the case law of the boards of appeal, late-filed material may be rejected even if it was possibly highly relevant, if its late-filing constitutes an abuse of the procedure (c.f. Case Law of the Boards of Appeal of the European Patent Office, Chapter VI, F.3, 3.1.3). The respondent argues that the filing of document D9 during the appeal proceedings constituted an abuse because the legal successor of the proprietor of the patent derived from document D9, Baxter AG, belonged to the same group of companies as the appellant, Baxter Healthcare S.A.

3. Firstly, the fact per se that a cited document originates from the opponent itself or from a company associated with the opponent is, in the absence of evidence that the document was withheld deliberately, not an indication that the document was considered by the opponent when drafting its opposition. This view is in line with decision T 1019/92 of 9 June 1994, point 2.2 of the reasons.

4. Secondly, even if the appellant had been aware of document D9 when drafting the opposition, it would be plausible that the appellant would not have seen any reason to file it earlier because, as submitted by the appellant, it only became aware of a possible defect in the validity of the priority of the patent in suit after the end of the opposition proceedings. Thus, the late filing of document D9 seems to be the result of inattentiveness, rather than of deliberateness. Consequently, the late-filing of document D9 does not constitute an abuse of the procedure.

5. In conclusion, document D9 and document D10 cited to explain the term "EMD-TMAE-Fractogel®" in document D9 are admitted into the proceedings.

Remittal

6. Having decided to admit documents D9 and D10 into the proceedings, the question arises whether the board is to consider the documents and decide the case, or whether it should remit the case to the opposition division for consideration of the new material.

7. Article 111(1), second sentence, EPC stipulates that the boards of appeal may either exercise any power within the competence of the department which was responsible for the decision appealed or remit the case to that department for further prosecution. Thus, according to Article 111(1) EPC, the boards have a discretion in their decision to remit a case or not. In exercising this discretion the boards are, on the one hand, guided by the interest of the parties and the public in a speedy decision about the validity of a patent and, on the other, by the parties' interest in having the patent examined by two instances, although, as held in many decisions, according to the EPC, there is no right to have each issue examined by two instances. Moreover, in the case of late-filed material a further criterion to be observed is whether in accordance with Article 113(1) EPC the parties' right to be heard is safeguarded. Generally, the later in the proceedings material is filed and the more complex its examination is, the higher is the probability that there is not sufficient time left for the other party

to deal with that material adequately and that, consequently, the boards decide in favour of a remittal.

8. Documents D9 and D10 were filed by the appellant with the statement setting out the grounds for appeal, i.e. at the earliest point in time in appeal proceedings and less than two years before oral proceedings took place. Considering that this period was sufficiently long for the respondent and the board to study the documents and also taking into account that a possible consequence of remittal was further appeal proceedings on the issue of novelty, ensuing probably that a final decision on the validity of the patent would only be taken shortly before the end of the maximum patent term in 2012, the board has decided not to remit the case, but to decide on it itself.

Main request - claims as granted

Article 123(2) EPC

9. While claim 1 as filed is directed to "a process for recovering a highly pure virus-inactivated **factor VIII**", claim 1 as granted is directed to "a process for recovering a highly pure virus-inactivated **factor VIII/von Willebrand factor complex**". The appellant argues that this amendment results in subject-matter extending beyond the content of the application as filed.

10. A criterion for deciding whether or not an inadmissible amendment has taken place is whether a skilled person can derive the new subject-matter clearly and unambiguously from the application documents as filed

either explicitly or implicitly when reading the document with the common general knowledge.

10.1 The term "factor VIII/von Willebrand factor complex" is not explicitly mentioned in the application documents as filed.

10.2 On pages 4 to 14 of the application as filed details of the recovery process, for example the chromatographic material, starting material, buffers, etc. are disclosed. This description ends with the following summary:

"It is advantageous that in the process according to the invention the so-called von-Willebrand factor is not removed, but remains in the factor VIII fractions. Thus, it is possible to use the factor VIII preparations also for patients suffering from a deficiency in von-Willebrand factor. Furtheron [sic], factor VIII can also be employed in continuous-infusion techniques, due to the presence of the von-Willebrand factor which facilitates a natural stabilization of factor VIII."

In the board's judgement, a skilled person knew on the basis of his/her common general knowledge at the priority date of the patent in suit that factor VIII and von Willebrand factor existed as a complex in plasma and have been isolated therefrom as a complex (see for example document D8, page 139). He/she would thus consider that the requirement in the above passage of the application that the von Willebrand factor should not be removed (separated) from factor VIII can be equated to the description of a factor VIII/von

Willebrand factor complex. This skilled person's view would be supported by the statement at the end of the above-cited passage that the presence of von Willebrand factor facilitates natural stabilisation of factor VIII, an effect occurring if both molecular entities are complexed, a fact which the skilled person is aware of on the basis of his/her common general knowledge. Document D8 indeed reports for example on page 139 that: "FVIII and vWF circulate in plasma complexed to each other. All sized multimers of vWF appear to be involved (Davies et al, 1981). A role for vWF as a stabiliser for FVIII has been proposed (Weiss et al., 1977)."

Finally, the Table on page 20 of the application as filed, describing the presence of factor VIII and von Willebrand factor in preparations resulting from the disclosed process, would further support the above skilled person's view.

11. The appellant argues that in view of the greatly differing molecular weight of factor VIII and von Willebrand factor and in view of the teachings in document D3, the skilled person would consider it likely that by using an anion exchanger material and buffers with increasing ionic strength, factor VIII and von Willebrand factor would be separated rather than isolated as a complex.

12. However, the board notes that document D1 also discloses a process using an anion exchanger material and buffers with increasing ionic strength. But in contrast to the process of document D3, this process results in the recovery of a factor VIII/von Willebrand factor complex. Hence, the skilled person knows that

even by using apparently similar means - an anion exchanger for separation and buffers with increasing ionic strength - the product of the process may vary because it is dependent on the fine-tuning of further process conditions. Therefore, a skilled person would not have any reason to doubt the statements in the passage cited above and would understand the application as filed to disclose a process for recovering a factor VIII/von Willebrand factor complex.

13. By the same token and although the application as filed explicitly refers to "highly pure" in connection with "factor VIII", the skilled person would derive from the document that the process disclosed therein results in a "**highly pure** factor VIII/von Willebrand factor complex" in view of the passage on page 14 and the Table on page 20.

14. Hence the subject-matter of the claims as granted does not extend beyond the content of the application as filed. The requirements of Article 123(2) EPC are fulfilled and the ground of opposition under Article 100(c) EPC has to be rejected.

Novelty

Validity of the priority of the patent in suit

15. Pursuant to Article 87(1) EPC a right to priority can only be claimed in respect of the same invention. According to the opinion of the Enlarged Board of Appeal in G 2/98 (OJ EPO 2001, 413), the requirement for claiming priority of the "same invention" means that priority of a previous application in respect of a

claim in a European patent application (or patent) in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole. Therefore, in other words, all features by which an invention is characterised in a claim must be derivable from the priority document.

16. Claim 1 of the patent as granted is directed to a process for recovering a highly pure virus-inactivated factor VIII/von Willebrand factor complex from cryoprecipitate by means of anion exchanger chromatography, characterised in that a certain type of separating material as specified in the claim is used as anion exchanger material.

17. It is undisputed that the priority document explicitly discloses all features of claim 1 with the exception of the term "factor VIII/von Willebrand factor complex". Instead, the priority document refers to a process for recovering factor VIII. Moreover, the priority document neither comprises the passage on page 14 of the application as filed nor the Table on page 20 which, in the context of the assessment of Article 123(2) EPC, has been considered to represent an implicit basis for the term "factor VIII/von Willebrand factor complex" (see point 10.2 above).

18. The respondent's main argument is that a skilled person, knowing that in human blood plasma factor VIII and von Willebrand factor exist as a complex, would understand a claim covering a process for the preparation of factor VIII as being implicitly directed to a process

for recovering factor VIII/von Willebrand factor complex.

19. The board accepts that at the priority date a skilled person was aware of the fact that factor VIII and von Willebrand factor existed as a complex in plasma and that this complex could be isolated (see document D8, for example on page 136). However, the skilled person also knew that von Willebrand factor and factor VIII could be recovered as individual molecular entities. On page 133 of document D8 it is reported that factor VIII "virtually free of von Willebrand factor" had been produced and on page 136, purification of von Willebrand factor is described. It is also disclosed that initial purifications of von Willebrand factor actually resulted in the factor VIII/von Willebrand factor complex and that methods of separation of the two entities were known (page 136).

20. Thus, given the structural difference between the three entities, given an existing terminology for the three structural alternatives and given that preparation processes for all of them were known, the board considers that there was no reason for the skilled person to give an interpretation to the term "factor VIII" in the priority document that deviated from its explicit meaning. Hence, the skilled person would have taken the term "factor VIII" in the priority document as it stood.

21. The board has furthermore given thought to the possible arguments that, firstly, the indication of the end result of the claimed process ("for recovering a highly pure virus-inactivated factor VIII/von Willebrand

factor complex") is not a true technical feature, but only the illustrative indication of its purpose and, secondly, even if it were a true technical feature, that the different characterisation of the end product in the priority document and claim 1 as granted does not matter because the claimed process necessarily results in the factor VIII/von Willebrand factor complex.

21.1 As to the first argument, the board considers that, generally, features in a claim covering a manufacturing process, including those indicating the product to be manufactured, have to be regarded as true technical features of a claim which may not be neglected for its interpretation (see for example decision T 5/90 of 27 November 1992). This holds particularly true in the present case where, if the features specifying and characterising the end product were to be disregarded, the claimed process would only be defined by its starting product (cryoprecipitate) and the use of a certain chromatographic material, thus resulting in a claim covering various processes for the recovery of many different products, i.e. also products totally unrelated to factor VIII. Hence, since the indication of the product to be recovered has a limiting effect on the scope of the claim, it is a distinguishing feature.

21.2 As to the second argument, the board holds that there may be cases where the process steps of a manufacturing process are characterised in a claim in such a precise and complete way that their execution according to the indications in the claim inevitably and recognisably results in a specific product. In these cases, a difference in the nomenclature of the product, for

example, between the priority document and a claim at hand may indeed not have negative consequences. However, the present case is different because the features of the claimed process are not sufficiently precise and complete as to allow the assumption that carrying out the process without the knowledge of the product to be recovered would necessarily lead to the undissociated factor VIII/von Willebrand factor complex.

22. Consequently, the skilled person would derive from the priority document that the process disclosed therein is for the preparation of factor VIII, while the process as claimed is for the preparation of the complex of factor VIII and von Willebrand factor. Thus, since the subject-matter of the claim cannot be derived from the priority document, the inventions disclosed in the priority document and claimed in the patent in suit are not the same. All of the claims of the patent being directed to a process for recovering factor VIII/von Willebrand factor complex, none of them can validly claim the priority of document DE 4204694.

Document D9

23. Pursuant to Article 54(3) EPC in connection with Article 89 EPC, the content of a European patent application as filed, of which the date of priority is prior to the date of priority of the European patent or patent application to be examined and which is published under Article 93 EPC on or after that date, is to be considered as comprised in the state of the art.

24. The appellant's objection is that the content of document D9 prejudices the novelty of claim 1 pursuant to Article 54(3) EPC. As evidence of the content of this document, the published European patent, i.e. EP-B-567 448, instead of the application document was, as the board assumes, erroneously, filed by the appellant. In order to avoid confusion, any reference to document D9 will henceforward relate to the European patent application as filed.

25. Document D9 claims the priority date of 24 April 1992 of the Austrian application AT 849/92. Hence, it is relevant as state of the art pursuant to Article 54(3) EPC only if the priority is validly claimed. The validity of the priority has not been contested by the respondent. The board is satisfied that the subject-matter disclosed in the passages of document D9 which are relevant for the objection of lack of novelty is also disclosed in the Austrian priority application.

26. In the description of the patent in suit in paragraph [0037] reference is made to an ion exchanger material "known by the trade name of EMD-TMAE-Fractogel (M) 650".

26.1 Document D10 is a product description of the firm Merck entitled "Biochromatographie Trennung von Biopolymeren" which contains, after a short introduction on the separation of biomolecules by chromatography and a comparison of the functioning of conventional and tentacle-type ion exchanger, lists of the commercially available materials for biochromatography. Amongst the listed tentacle-type ion exchanger materials is a product designated "Fractogel® EMD TMAE-650 "which is available with two different particle sizes, i.e. "(S)"

and "(M)". Hence, one of the commercially available materials disclosed in document D10 is "Fractogel® EMD TMAE-650(M)". Thus, the name of the material as used in the patent in suit ("EMD-TMAE-Fractogel (M) 650") and in document D10 ("Fractogel® EMD TMAE-650(M)") differs in the order of the single terms of the product designation. Nevertheless, there is in the board's judgement no doubt that the patent in suit and document D10 refer to the same material.

26.2 The patent in suit relates to a process for recovering a highly pure, virus-inactivated factor VIII/von Willebrand factor complex from cryoprecipitate by means of an anion exchanger material characterised in claim 1 by a generic formula. In the context of the worked examples a specific ion exchanger material is not described. Instead, the only passage in the patent document where a specific material is referred to, is the one already mentioned in point 26 above, i.e. paragraph [0037]. It is stated that "(t)he sample is charged onto a chromatography column containing the gel permeation material known by the trade name of EMD-TMAE-Fractogel (M) 650, which material exhibits ion exchanger activity." Although the disclosure of a process step and the specific material used therefor in the general part of the patent document without repetition of it in the part setting out the examples may be considered as an unusual way of presentation, a skilled person would nevertheless understand, given that only one type of specific material is referred to and in view of the specific way in which the step is disclosed, that this is the ion exchanger material on which the cryoprecipitate is charged in the worked examples. Hence, the skilled person would regard the

ion exchanger material termed "EMD-TMAE-Fractogel (M) 650" as representing a compound falling under the generic formula recited in claim 1. The board notes that during the proceedings the respondent has never argued to the contrary.

26.3 According to the process reported in Example 2 of document D9, the pre-purified cryoprecipitate is applied to "EMD-TMAE Fractogel® (Fa. Merck)" resulting in a "Faktor VIII-hältige Fraktion" which is then ultrafiltrated, lyophilised and heated for virus inactivation.

26.4 A first question to be answered in the assessment of novelty is whether the material according to Example 2 of document D9 falls under the definition of the anion exchanger material according to claim 1 of the patent as granted. If "EMD-TMAE Fractogel®" referred to in document D9 was the type of material disclosed in document D10 ("Fractogel® EMD TMAE-650") it would likewise be a material according to the patent in suit (see point 26.1 above) and therefore comprised by the generic definition in claim 1 (see point 26.2).

26.5 The board is convinced that the skilled person would understand the reference in Example 2 of document D9 to "EMD-TMAE Fractogel®" as a sloppy, shortened form of the correct trade name "Fractogel® EMD TMAE-650 because, as is apparent from document D10, the product termed "Fractogel® EMD TMAE-650" was the only commercially available ion exchanger material of the company Merck" comprising the three terms EMD, TMAE and Fractogel in its name. Therefore, it is concluded that the material designated "EMD-TMAE Fractogel®" in document D9 would be

understood as being the same material as "Fractogel® EMD TMAE-650" referred to in document D10.

26.6 It is noted that, in contrast to the patent in suit, document D9 is silent as to the particle size of the ion exchanger material. This is however irrelevant in the assessment of novelty, because the definition of the ion exchanger material in claim 1 of the patent as granted likewise does not contain any indication of the size of the material, i.e. it includes particles of any size.

26.7 Thus, it is concluded that the material "EMD-TMAE Fractogel" in document D9 falls under the terms of the Markush formula in claim 1 as granted. The respondent has not argued to the contrary.

27. It remains to be determined what is the nature of the end product of the process according to Example 2 in document D9, bearing in mind that the preamble of claim 1 of the patent as granted is formulated as a "process for recovering a highly pure virus-inactivated factor **VIII/von Willebrand factor complex**" (emphasis added).

27.1 In Example 2 of document D9 the resulting product is characterised as a "Faktor VIII-hältige Fraktion", a wording which may prima facie be interpreted either as a fraction including factor VIII alone or as including the complex of it with von Willebrand factor. However, it is stated in column 3, lines 7 to 11, of document D9 that: "Faktor VIII kann erfindungsgemäß als FVIII/vWF-Komplex, FVIII bzw. vWF hergestellt werden. Während des Herstellungsverfahrens kann etwa eine Behandlung zur

Dissoziation des FVIII/vWF-Komplexes vorgenommen werden, z.B. mit Calciumchlorid." The absence of the disclosure of any such dissociation step in Example 2 leads the board to the conclusion that the process described therein results in a factor VIII/von Willebrand factor complex.

27.2 Virus inactivation of the obtained fraction is, according to Example 2, carried out by heating in a closed container for 10 hours at 60°C.

28. In summary, the starting material is cryoprecipitate according to the process disclosed in document D9 as well as in claim 1 of the patent as granted. The anion exchanger material used in the process of document D9 falls under the definition of anion exchanger materials of claim 1. The product resulting from this process is a virus-inactivated factor VIII/von Willebrand factor complex. In view of the above, the board concludes that the process disclosed in Example 2 of document D9 has all features according to the process of claim 1 and therefore prejudices the novelty of its subject-matter.

29. The subject-matter of claim 1 of the patent as granted does not fulfil the requirements of Article 54 EPC so that the respondent's main request has to be refused.

Auxiliary Request I

Articles 123(2) and (3), 84 and 54 EPC

30. Claim 1 of auxiliary request I is a combination of claim 1 and dependent claim 4 as granted. Claim 1 as granted does not violate Article 123(2) EPC (see point 14 above). The features of claim 4 as granted are

identically present in claim 6 as filed (see sections II and III above), a claim which was dependent on claim 1 as filed. Therefore, the board concludes that the combination of these features neither results in subject-matter extending beyond the content of the application as filed nor extends the protection conferred.

Hence, the requirements of Article 123(2) and (3) EPC are met.

31. Objections under Article 84 EPC were not raised by the appellant. The board notes that in claim 1, the expression "purification of factor VIII" ("... wherein the purification of **factor VIII** is effected by washing and eluting with buffers...") may be regarded as being in contradiction with the preamble of the claim referring to recovering a **factor VIII/von Willebrand factor complex**. However, the same combination of wording was already present in dependent claim 4 as granted if read together with claim 1 as granted. Thus, the potential lack of clarity which appears to be the result of an oversight at the grant of the patent, is not caused by an amendment and therefore not open to an objection under Article 84 EPC. Furthermore, in view of the whole disclosure in the patent in suit the board interprets the term "factor VIII" in the characterising part of claim 1 to mean "factor VIII/von Willebrand factor complex".

32. Objections under Article 54 EPC were not raised by the appellant and the board also does not see any.

Article 83 EPC

33. The board has considered two lines of argument in the context of Article 83 EPC:

Firstly, the appellant argues that the term "highly pure" is so ambiguous that a skilled person does not know which type of product is to be prepared and that therefore the requirements of Article 83 EPC are not met. Thus, a question to be answered in relation to this argument is whether the term "highly pure" is indeed ambiguous.

33.1 The definition of a feature in a patent claim by a term is considered unclear if such definition cannot be understood by the skilled reader of the claim in the context of the whole disclosure in the patent. For this reason, terms which may seem ambiguous per se because, for example, they do not have a precise art-recognised meaning or because they are relative terms, may nevertheless be considered as clear and therefore be accepted in patent claims (for example, decision T 649/97 of 8 December 2000, point 1 of the reasons - "transparent").

33.2 The board agrees that the term "highly pure" per se does not have a precise meaning. However, in the Table on page 7 of the patent in suit a product is characterised. Although it is obtained after carrying out a process no longer falling under claim 1 of the auxiliary request, its properties may nevertheless be taken into consideration in order to illustrate the meaning of the term. This is, because the end product is the same independently of the process, i.e. it is a

"highly pure ... factor VIII/von Willebrand factor complex" (see claim 1 of auxiliary request I and claim 1 as granted). The parameters given in the table are all suited to characterise the purity of a product: the concentration of factor VIII, von Willebrand factor and of other proteins are given as well as the total protein content allowing in combination with the concentration of the specific protein the calculation of the specific activity of a protein which may be taken as a further indication of the degree of purity. Hence, a skilled person can derive the meaning of the term "highly pure" in the context of the patent in suit from its disclosure. Therefore, in contrast to the appellant's view, the term is not unclear. Consequently, the objection under Article 83 EPC based on the lack of clarity of this term fails.

34. Furthermore, the board notes that in the context of an objection of lack of inventive step the appellant argued that the skilled person was not able to obtain all embodiments falling under the claim and referred to the experiments in Annex 1 in order to show that the "intended effect" of the claimed process, i.e. recovering factor VIII/von Willebrand factor complex could not be achieved at any combination of concentrations of salt in the washing and eluting buffers disclosed in the patent in suit. However, since the recovery of the complex is to be regarded as a true and therefore limiting technical feature of the claim (see point 21.1 above), this argument needs to be considered in the context of Article 83 EPC. Thus, the question arising is whether the experiments referred to by the appellant are suited to demonstrate that the

skilled person would not be able to carry out the process as claimed successfully without undue burden.

34.1 It is pointed out in many decisions of the boards of appeal that an objection of lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts (for example T 19/90, OJ EPO 1990, 476). In the present case, however, the board considers that the experiments in Annex 1 are not suitable for challenging the sufficiency of disclosure of the subject-matter of the present claims, for the following reasons:

34.2 Claim 1 requires that the purification of factor VIII/von Willebrand factor complex is "effected by washing and eluting with **buffers** having subsequently increasing ionic strengths, characterized in that the ionic strength of **the buffer** is adjusted by means of quaternary ammonium salts ....". Thus, the term "buffer" is used once in the plural form and once in the singular form, leading to an ambiguity as to the minimum number of buffers to be adjusted with the quaternary ammonium salt, i.e. whether it is at least one or all of them.

34.3 However, in view of the use of the definite article ("**the** buffer") in contrast to a wording such as "**a** buffer" or "**one of the** buffers" and in view of the examples describing the use of the same salt (although in the specific examples it is sodium chloride and not a quaternary ammonium salt as claimed) for the adjustment of the ionic strength of buffer A, B and C, i.e. **all** buffers, the board is convinced that the latter construction, i.e. the mandatory presence of

quaternary ammonium salts in each of the buffers, applies.

34.4 During all process repetitions according to Annex 1 either a quaternary ammonium salt (choline chloride, betaine hydrochloride; Examples 2.1a, 2.1b and 2.2) is only used in **one** of the buffers, while in the other two sodium chloride is used, or such a salt is **not** used at all (Example 2.3). Therefore, the experiments do not reflect the claimed process and are therefore not suitable for substantiating doubts of lack of enablement of the subject-matter of the claims of auxiliary request I.

35. The requirements of Article 83 EPC are thus fulfilled.

Inventive step

36. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal consistently apply the problem and solution approach requiring as the first step, prior to the formulation of the technical problem to be solved and the evaluation of the obviousness of the solution provided, the identification of the closest prior art, i.e. a document providing the most promising springboard to the invention.

37. Document D1 was considered as the closest prior art document by the appellant, while the respondent preferred document D3.

38. The boards of appeal have developed in their case law criteria for identifying the closest prior art document.

It has been repeatedly pointed out that it should be a document relating to subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3).

39. When these criteria are applied to documents D1 and D3, document D1 turns out to be the closest prior art document because it describes a process for recovering a **factor VIII/von Willebrand factor complex**. In contrast, the board considers that the skilled person would infer from the disclosure of document D3 that the process disclosed therein aims at **separating** factor VIII from von Willebrand factor, because it is emphasised in several passages in the document that the choice of the specific anion exchange material results in separation of factor VIII from other proteins, inter alia von Willebrand factor (see for example column 3, lines 21-32, column 4, line 57, column 5, lines 53-55).

40. In the context of the assessment of inventive step of the claims as granted, the opposition division concluded in view of the specific activity of factor VIII calculated according to results presented in the Table on page 7 of the patent in suit (67.5 IU/mg) and the specific activity of factor VIII disclosed in document D1 (10-30 IU/mg), that the problem to be solved was the provision of an **improved** process for the preparation of a factor VIII/von Willebrand factor complex.

40.1 The subject-matter of the claims of auxiliary request I is restricted compared to the claims as granted in that

it is specified that the ionic strength of the washing and eluting buffers is adjusted with a quaternary ammonium salt, as defined in the claim, alone or in combination with common salt. However, the results shown in the Table on page 7 were obtained by using a process alternative which is not covered by the present claims, i.e. the ionic strength of all buffers is adjusted with sodium chloride alone (see points 33.2 and 34.3 above). Moreover, an improvement achievable with the claimed process over that disclosed in the closest prior art document D1 is also not derivable from the generic disclosure of the patent in suit.

Hence, the board considers that the objective problem underlying the subject-matter of claim 1 of auxiliary request I is the provision of an **alternative** process for recovering a factor VIII/von Willebrand factor complex.

41. On the interpretation of the claim as set out in point 21.1 above and in view of the conclusions reached with respect to sufficiency of disclosure under Article 83 EPC (see points 33 to 35 above), the board concludes that the whole subject-matter as claimed has to be regarded as a solution to this problem.

42. Document D1 discloses a process for recovering a highly pure virus-inactivated factor VIII/von Willebrand factor complex from blood plasma by means of an anion exchange chromatography. As anion exchange material it is inter alia suggested using a "tentacle type" anion exchanger (column 6, lines 49-56) as used in the method according to claim 1 of the patent in suit. The ionic strength of the washing and eluting buffers is set with

sodium chloride. Thus, the subject-matter of claim 1 is distinguished from the subject-matter disclosed in document D1 in that cryoprecipitate is the starting material and in that "(t)he purification of factor VIII is effected by washing and eluting with buffers having subsequently increasing ionic strengths, the ionic strength of the buffer is adjusted by means of quaternary ammonium salts having at least one hydrocarbyl chain having from 1 to 6 carbon atoms and bearing a hydrophilic substituent alone or in combination with common salt."

43. In the assessment of inventive step the question to be answered is whether or not a skilled person seeking to provide an alternative method to that disclosed in the closest prior art document D1 would have been led by teachings in that document and/or in other prior art documents to modify the method of document D1 by choosing the above-mentioned distinguishing features.

44. As to the starting material, cryoprecipitate has always been considered as a suitable source for the purification of factor VIII/von Willebrand factor complex (see references to earlier publications in the introductory part of document D1, column 1, lines 31-40). In contrast, document D1 teaches not using cryoprecipitate as starting material in order to reduce the loss of factor VIII by the step of cryoprecipitation and in order to simplify the process. However, bearing in mind that in the present case the problem to be solved is the provision of an **alternative** process for the preparation of factor VIII/von Willebrand factor complex and seeing that the reasons given in document D1 for not using cryoprecipitate are

not related to the unsuitability of the material in general, but to making the process more economic, the board has doubts that the disclosure in document D1 had led the skilled person to categorically discard cryoprecipitate as a starting material for the recovery of factor VIII/von Willebrand factor complex. However, in view of the findings below, the board will not amplify this point.

45. With regard to the use of a quaternary ammonium salt, as defined in the claim, alone or in combination with common salt for adjusting the ionic strength of the buffers, the appellant argues that this use is common general knowledge.

46. However, none of the documents on file published before the priority date of the patent in suit and dealing with the preparation of factor VIII or factor VIII/von Willebrand factor complex by anion exchange chromatography - be it patent documents such as D1, D3, D4 or review-type articles such as document D8 or documents dealing with tentacle-type anion exchange materials as referred to in claim 1 such as documents D2 and D10 or protein separation therefrom such as document D7 - teaches quaternary ammonium salts having at least one hydrocarbyl chain with from 1 to 6 carbon atoms and bearing a hydrophilic substituent as constituents of washing or eluting buffers. This is particularly remarkable in the case of documents D1 and D2 disclosing worked examples in which the chromatography material referred to in claim 1 is used for the preparation of factor VIII/von Willebrand factor complex (document D1) or other proteins (document D2). Document D7 reports a comparison of the

effect of NaCl or KBr in elution buffers on the retention behaviour of proteins during elution from tentacle-type anion exchangers.

47. Hence, this evidential situation leads the board to the conclusion that the use of washing and eluting buffers comprising quaternary ammonium salts having at least one hydrocarbyl chain having from 1 to 6 carbon atoms and bearing a hydrophilic substituent cannot be regarded as belonging to the common general knowledge.

48. Furthermore, the remaining documents on file neither disclose nor suggest the use of such quaternary ammonium salts either.

49. Consequently, the board concludes that choosing quaternary ammonium salts of the type referred to in claim 1 for setting the ionic strength of washing and eluting buffers instead of sodium chloride as in document D1 in the context of a process for recovering a factor VIII/von Willebrand factor complex is not obvious.

50. An inventive step is acknowledged for the subject-matter of claim 1 as well as for that of dependent claims 2 to 5. The subject-matter of the claims of auxiliary request I complies with the requirements of Article 56 EPC.

Adaptation of the description

51. The amended description filed by the respondent at the oral proceedings does not give rise to any objections under the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent in amended form on the basis of the following documents:

   – claims 1 to 5 of auxiliary request I filed in the oral proceedings

   – adapted description (pages 2 to 7 of the patent specification, including page 5a) filed in the oral proceedings.

Registrar: Chair:

P. Cremona R. Moufang