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**Datasheet for the decision
of 4 April 2017**

Case Number: T 2413/13 - 3.3.04

Application Number: 08380326.2

Publication Number: 2078730

IPC: C07K14/755, A61K38/37

Language of the proceedings: EN

Title of invention:

Process for obtaining a concentrate of von Willebrand factor or a complex of factor VIII/ von Willebrand factor and use of the same

Patent Proprietor:

Grifols, S.A.

Opponents:

Baxter International Inc.
CSL Behring GmbH

Headword:

Von Willebrand factor concentrate/GRIFOLS

Relevant legal provisions:

EPC Art. 56
RPBA Art. 13(3)

Keyword:

Main request, auxiliary requests I, III to VII - inventive step
(no)
auxiliary request II - admitted (no)

Decisions cited:

T 0091/98, T 1045/98

Catchword:



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Case Number: T 2413/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 4 April 2017

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Decision under appeal: **Interlocutory decision of the Opposition**
Division of the European Patent Office posted on
10 October 2013 concerning maintenance of the
European Patent No. 2078730 in amended form.

Composition of the Board:

Chairman B. Claes
Members: R. Morawetz
 M. Blasi

Summary of Facts and Submissions

- I. The appeals filed by opponent 01 (hereinafter "appellant I") and opponent 02 (hereinafter "appellant II") lie from the opposition division's interlocutory decision concerning maintenance of European patent No. 2078730 in amended form. The patent is entitled "*Process for obtaining a concentrate of von Willebrand factor or a complex of factor VIII/ von Willebrand factor and use of the same*".
- II. The patent was opposed under Article 100(a) EPC for lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) and Article 100(c) EPC.
- III. The opposition division decided that, while the subject-matter of claim 1 of the main request lacked novelty (Article 54 EPC) and claim 1 of auxiliary request 1 lacked clarity (Article 84 EPC), the set of claims in auxiliary request 2 fulfilled the requirements of the EPC.
- IV. The following documents are referred to in this decision:
- D1 Furuya K. *et al.*, *Vox Sanguinis* (2006), vol. 91, pages 119-125.
- D2 Chtourou S. *et al.*, *Vox Sanguinis* (March 2007), vol. 92, pages 327-337.
- D3 Burnouf T. and Radosevich M.; *Haemophilia* (2003), vol. 9, pages 24-37.

- D5 US2007/0275880, 29 November 2007
- D8 Mazurier C. *et al.*, *Vox Sanguinis* (2004), vol. 86, pages 100-104.
- D16 Factor VIII - von Willebrand Factor, vol. 1, Seghatchian M.J. and Savidge G.F., editors, (1989), chapter 3, pages 41 to 81.
- D26 Registry of clotting factor concentrates, Kasper C.K. and Costa e Silva M., editors, 5th edition (2004), pages 1 and 2; Tables 1A, 1B, 2, 3, 4, 5, and 6.
- V. Among the objections raised by the appellants in their respective statements of grounds of appeal was that a process for obtaining a concentrate of Von Willebrand Factor (VWF) lacked inventive step in view of the teaching of document D8 in combination with the disclosure of document D1 (see paragraphs 98 to 123 and paragraph VI.1, respectively).
- VI. With its reply to the statements of grounds of appeal the proprietor (hereinafter "respondent") resubmitted the set of claims in auxiliary request 2, which had been considered allowable by the opposition division, as its main request and further sets of claims as auxiliary requests I, II, III-A, III-B, IV-A and IV-B.
- VII. The board summoned the parties to oral proceedings. Subsequently, it issued a communication pursuant to Article 15(1) RPBA in which it indicated, *inter alia*, that it was inclined to agree with the construction given to claim 1 of the main request in the decision under appeal (see points 9 to 12 of the board's

communication).

VIII. Oral proceedings before the board took place on 4 April 2017. In the course of the oral proceedings the respondent renumbered its pending auxiliary requests (see section VI above) such that auxiliary request IV-A became auxiliary request I and auxiliary requests I, II, III-A, III-B and IV-B became auxiliary requests III to VII. It further filed a new auxiliary request II.

Claim 1 of the main request reads as follows:

"1. A process for obtaining a concentrate of Von Willebrand Factor or a complex of Factor VIII/Von Willebrand Factor of human or recombinant origin, characterised by:

a) preparation of a solution of (1) Von Willebrand Factor, or (2) a complex of Factor VIII/Von Willebrand which contains VWF in a concentration of up to 12 IU VWF:RCo/ml and a proportion of activities between Von Willebrand Factor/Factor VIII of 0.4 or more, wherein activity of the VWF is based on the role of VWF as a cofactor for the antibiotic Ristocein (VWF:RCo) in its ability to induce platelet aggregation (Pharmacopoeia Europea 07/2006:20721) and activity of FVIII relates to the coagulating activity of FVIII (FVIII:C) which is based on the role of FVIII as a cofactor in the activation of VX in the presence of FIXa, calcium ions and phospholipids (Pharmacopoeia Europea 07/2006:20704),

b) nanofiltration of the solution prepared in a) through a filter having a pore size of 20 nanometers, at a maximum pressure of less than or equal to 0.5 bar, in the presence of calcium ion and at a pH greater than

5.5."

Claim 1 of auxiliary request I differs from claim 1 of the main request in that the maximum pressure is required to be less than 0.5 bar, the concentration of calcium ion in the solution undergoing nanofiltration varies between 0.05 and 0.2 M and the process is for the production of a filtrate that is suitable for the treatment of von Willebrand disease.

Claim 1 of auxiliary request II differs from claim 1 of auxiliary request I in that the embodiment relating to obtaining a concentrate of VWF has been deleted.

Claim 1 of auxiliary request III differs from claim 1 of the main request in that the maximum pressure is required to be less than 0.5 bar.

Claim 1 of auxiliary request IV differs from claim 1 of auxiliary request III in that the term "solution" is inserted after "which" and before "contains".

Claim 1 of auxiliary request V differs from claim 1 of auxiliary request III in that the concentration of calcium ion in the solution undergoing nanofiltration varies between 0.05 and 0.2 M.

Claim 1 of auxiliary request VI corresponds to claim 1 of auxiliary request V except that the term "solution" is additionally inserted after "which" and before "contains".

Claim 1 of auxiliary request VII corresponds to claim 1 of auxiliary request I except that the term "solution" is additionally inserted after "which" and before "contains".

At the end of the oral proceedings the chairman announced the board's decision.

- IX. The appellants' arguments relevant for the present decision may be summarised as follows:

Main request

Claim construction - claim 1

The limitation "*which contains VWF in a concentration of up to 12 IU VWF:RCo/ml and a proportion of activities between Von Willebrand Factor/Factor VIII of 0.4 or more*" (hereinafter "*which clause*") applied only to the feature "*(2) a complex of Factor VIII/Von Willebrand*" for the following reasons:

Grammatically, the comma after the term "*(1) Von Willebrand Factor*" indicated a separation from the "*which clause*". The word "*which*" referred back to the solution containing the Von Willebrand Factor/Factor VIII (VWF/FVIII) complex since there was no comma after "*Factor VIII/Von Willebrand*".

It also made technical sense to distinguish the embodiment relating to VWF from the embodiment relating to the complex of FVIII and VWF, so the proportion of activities between VWF/FVIII could apply only to that second embodiment.

There had to be some measurable amount of FVIII in the solution for the "*which clause*" to apply. If no FVIII was present in the solution, division by zero would result in an undefined proportion of activities.

Inventive step - claim 1

Document D8 was the closest prior art for the embodiment of claim 1 relating to VWF. It related to the same technical area, i.e. the removal of viruses from VWF preparations, and disclosed purification of VWF wherein the preparation was filtered through a filter with a pore size of 35 nm at a pressure of 200 ± 50 mbar, which was less than 0.5 bar (see page 102, left-hand column, first paragraph). Document D8 taught that a 35 nm pore size filter was not capable of removing small non-enveloped viruses effectively and so provided the skilled person with the motivation to modify and optimise the method it disclosed.

The features that distinguished the claimed invention from the teaching of document D8 were that a 20 nm filter was used instead of a 35 nm filter and that nanofiltration was carried out in the presence of calcium ions and at a pH of greater than 5.5. The last two features were not associated with any technical advantage and could thus be ignored when defining the technical problem.

The technical effect of using a smaller pore size for filtration was the removal of small non-enveloped viruses between 20 nm and 35 nm of size.

The problem to be solved was how to obtain a preparation of VWF that was free of small non-enveloped viruses with a diameter of between 20 and 35 nm.

The skilled person looking for a method of removing the smaller non-enveloped viruses would have referred to

document D1 since this document disclosed a purification method that removed non-enveloped viruses passing through a 35 nm filter. Filtration using a 20 nm pore size filter in document D1 was effective in removing almost all tested viruses, including small non-enveloped viruses, and the document's authors stated that this process could add a marked degree of viral safety (see abstract; Table 3 and last paragraph on page 125). Thus, the skilled person would have been motivated to use the 20 nm filter for efficiently removing small non-enveloped viruses from VWF preparations.

What was relevant to the skilled person was that document D1 disclosed the successful implementation of a 20 nm nanofiltration of a solution containing VWF, not whether or not such a product was useful in treating von Willebrand disease (VWD).

Document D1 was silent on functional (in)activity of VWF after filtration. A conformational change explained how it passed through the 20 nm filter (see page 125, left-hand column, first paragraph) but nothing in document D1 indicated that a conformational change impaired the activity of VWF. Rather, as a consequence of the affinity purification step, the amount of VWF obtained in document D1 was too little to be suitable for the treatment of VWD. Hence, document D26 referred to it as non-functional, but this was unrelated to the filtration itself. The little amount of VWF in the product of document D1 had passed unchanged through the 20 nm filter, as demonstrated in Figure 4.

Document D8 disclosed 35 nm filtration of a solution containing a high VWF concentration resulting in a high-activity VWF product. Document D1 disclosed that

VWF passed equally well through filters with a pore size of 20 nm as through filters with a pore size of 35 nm, without any alteration of its content and multimeric structure (page 123, paragraph bridging left and right-hand column; Figure 4 and page 124, right-hand column, last paragraph). Accordingly, if the 35 nm VWF product was functional, then the skilled person would expect the same of the 20 nm product.

This would not change in view of the statement in document D16 about the importance of multimeric forms of VWF or the statement in document D3 that filtration of VWF through 35 nm filters was possible. Document D3 did not state that filters with a smaller pore size would not work. It was a review article published three years before document D1, which demonstrated that VWF could pass a 20 nm filter.

The disclosure in document D2 that filtration of VWF through membranes with a pore size of 15 nm led to a reduction in high-molecular-weight VWF multimers by half (see page 332, right-hand column, second paragraph) did not permit conclusions with regard to filters of a pore size of 20 nm.

Thus, the skilled person would have used as starting material a VWF solution as disclosed in document D8 in combination with the 20 nm filter disclosed in document D1, since it was shown to be superior for virus safety and suitable for the filtration of VWF.

Document D8 described a successful nanofiltration of VWF using a 35 nm filter under a constant working nitrogen pressure of 200 ± 50 mbar, while the pressure conditions in document D1 were optimised for the nanofiltration of FVIII, which was less sensitive to

shear stress than VWF. Moreover, the skilled person would adapt the conditions disclosed in document D8 to those disclosed in document D1 as suitable for filtration, i.e. 40 mM Ca and a pH of 6.35 (see page 120 right-hand column, first paragraph).

Auxiliary request I

Inventive step - claim 1

Document D8 was still the closest prior art for the subject-matter of claim 1 as it related to the purification of VWF for the treatment of VWD.

Starting from the VWF-containing solution suitable for the treatment of VWD disclosed in document D8, in the same way as for claim 1 of the main request, the skilled person faced with the problem of providing a VWF-containing solution that was free of small non-enveloped viruses would have considered and applied the teaching of document D1. This document provided the skilled person with sufficient technical information to know that filtration of a solution containing VWF was feasible and would lead to a functionally active VWF solution.

The skilled person would have had no reason to be sceptical, as the suitability of the VWF product for the treatment of VWD could be ascertained by routine *in vitro* assays.

Auxiliary request II

Admission into the appeal proceedings

The request had been filed late during the oral

proceedings and should not be admitted into the appeal proceedings. Both appellants had argued in their statements of grounds of appeal that the first embodiment of claim 1 of the main request lacked inventive step over the combination of the disclosures in documents D8 and D1, and the focus in the written proceedings had not been on the second embodiment of claim 1 of the main request.

The board's construction of claim 1 of the main request was the same as that in the opposition division's decision. The board had already indicated this in its communication. The auxiliary request could thus have been filed earlier.

The appellants had prepared for the oral proceedings on the basis of the requests on file. It would be unfair on them to have to deal with a request from which the first embodiment was deleted without an adjournment of the oral proceedings and an adjournment to the next day was not sufficient.

Auxiliary requests III to VII

Inventive step - claim 1

No arguments in addition to those submitted for the main request and auxiliary request I, respectively, were submitted.

- X. The respondent's arguments relevant for the present decision may be summarised as follows:

Main request

Claim construction - claim 1

The VWF in (1) of claim 1 was limited by the wording relating to concentration and proportion in subpart (a) of claim 1 because the word "*which*" referred back to the solution - not to the complex of FVIII/VWF - and the solution comprised both VWF and FVIII/VWF.

For a VWF solution without any FVIII, the proportion of activities expressed relative to FVIII was infinite and thus larger than 0.4. Therefore, it was not inconsistent to define a solution containing only VWF as an activity proportion with FVIII.

Since a higher concentration resulted in too high a viscosity of the VWF solution to be filtered the solution of VWF was limited by the concentration limitation referred to in the claim.

Although claim 1 was not limited to the intended therapeutic use of VWF, the intended purpose was nevertheless of relevance for the selection of the closest prior art.

Inventive step - claim 1

Document D8 was specifically directed to obtaining a therapeutic concentrate of VWF for use in the treatment of VWD and was the closest prior art for the first embodiment of claim 1. VWF was nanofiltered using

membranes having a pore size of 35 nm.

The subject-matter of claim 1 differed in that a filter with a pore size of 20 nm was used in combination with a particular pH and in the presence of calcium ions, the effect of which was that an improved concentrate of VWF was obtained which was safer than previous concentrates as it was free of small non-enveloped viruses with a diameter between 20 and 35 nm.

The importance of the presence of calcium ions and of the pH was explained in the patent in paragraph [0036].

The problem to be solved was the provision of a process for obtaining a VWF concentrate with improved safety.

The skilled person wishing to prepare VWF with improved viral safety would not have considered the disclosure in document D1, because it related to a concentrate of FVIII rather than of VWF. The product described in document D1, Cross Eight M[®], did not contain any functional VWF and thus was not suitable for the treatment of VWD (see document D26, Table 3).

Document D16 similarly stated that commercial FVIII compositions, except those specially prepared to retain all VWF forms, were of limited efficacy in the treatment of VWD (page 43, second paragraph).

Furthermore, document D1 disclosed that the FVIII/VWF complex passed through the 20 nm filter only as a result of shear-dependent conformational change (page 125, left-hand column, first paragraph) and, while it mentioned that the multimeric structure of VWF was preserved in the filtration, Figure 4 showed that the filtrate contained only minor amounts of higher-molecular-weight multimers of VWF. The skilled person, however, knew that VWF had a multimeric structure, which was required for its efficacy.

Document D3 disclosed that VWF could only be filtered using 35 nm filters (see page 31, left-hand column, third paragraph). Furthermore, document D2 disclosed that filtration over a filter having a pore size of 15 nm led to a significant decrease in VWF multimers (see page 332, right-hand column, second paragraph).

Thus, in view of the knowledge that both VWF's multimeric forms and other structural features were important for its biological efficacy, document D1 would discourage the skilled person interested in obtaining a VWF product suitable for treating VWD from using a 20 nm filter.

The pressure used for filtration in document D1 was higher than that defined in claim 1. It was inconsistent to assert that the skilled person would maintain the pressure used in document D8 when replacing the filter of 35 nm with a filter of 20 nm but otherwise adopt the conditions taught in document D1 (the pH and presence of calcium ions). Document D1 was silent on the pressure used for the filtration of VWF.

Auxiliary request I

Inventive step - claim 1

Claim 1 now explicitly required that the product be suitable for the treatment of VWD. Since the product of document D1 was not suitable for this, the skilled person would not consult that document.

The skilled person would have no reasonable expectation that filtration through a 20 nm filter would result in

a product that was suitable for the treatment of VWD. There was a firm belief in the prior art that a filter with a pore size larger than 20 nm had to be used for the filtration of VWF (see document D3).

Auxiliary request II

Admission into the appeal proceedings

The deletion of the first embodiment relating to VWF from claim 1 was a simple amendment and should be admitted into the appeal proceedings. The arguments put forward in the written proceedings had mainly been against the embodiment relating to the second embodiment, i.e. the FVIII/VWF complex, while the debate in the oral proceedings had focused for the first time on the first embodiment relating to VWF. Although the request had admittedly been filed late, the board had discretion and should weigh up the interests of the parties. Adjournment of the proceedings to the next day would give the appellants time to prepare their case with respect to this claim request.

Auxiliary requests III to VII

Inventive step - claim 1

While the respondent provided an explanation of the amendments made in claim 1 of these requests in the written proceedings, no arguments were submitted either in writing or during the oral proceedings as to why these amendments would establish an inventive step.

- XI. The appellants requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeals be dismissed, i.e. that the patent be maintained in the amended form considered allowable by the opposition division (main request) or, alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims in auxiliary requests I to VII. Auxiliary request I had been filed as auxiliary request IV-A and auxiliary requests III to VII as auxiliary requests I, II, III-A, III-B and IV-B with the reply to the appeals, while auxiliary request II had been filed at the oral proceedings.

Reasons for the Decision

Main request

Claim construction - claim 1

1. The subject-matter of claim 1 encompasses two embodiments, the first referring to von Willebrand factor (VWF) and the second to a complex of Factor VIII/VWF (see section VIII).
2. The opposition division held that the limitation "*which contains VWF in a concentration of up to 12 IU VWF:RCo/ml and a proportion of activities between Von Willebrand Factor/Factor VIII of 0.4 or more*" applied only to the feature "(2) a complex of Factor VIII/Von Willebrand" and not to the alternative embodiment of claim 1 referring to VWF (see decision under appeal, page 3, third to fifth paragraph). The board agrees with this claim construction.
3. To the skilled reader of claim 1, the comma after the term "(1) Von Willebrand Factor" and before the wording

"or (2) a complex of Factor VIII/Von Willebrand" indicates a separation of the two embodiments, i.e. the first embodiment relating to VWF (hereinafter "the first embodiment") and the second embodiment relating to the FVIII/VWF complex (hereinafter "the second embodiment"). The features "*which contains VWF (...)*" and "*(2) a complex of Factor VIII/Von Willebrand*" are not separated by a comma. The word "*which*" would thus be understood by the skilled person to refer back to the solution containing the FVIII/VWF complex but not to the solution containing VWF.

4. This construction is supported by the skilled person's technical understanding: a defined proportion of activities between VWF and FVIII requires the presence of both VWF and FVIII, since the latter's absence would result in an undefined proportion of activities, i.e. not "*0.4 or more*".
5. The board was not persuaded by the respondent's argument that the concentration limitation mentioned in claim 1 also had to apply to the first embodiment because too high a concentration of VWF would result in too high a viscosity of the protein solution to be filtered and that, therefore, the opposition division's claim construction was wrong. The fact that the skilled person is free to choose the concentration of the VWF in the solution to be filtered does not mean that he would necessarily choose a concentration which is too high.
6. In the board's judgement, the first embodiment of claim 1 is thus directed to a process for obtaining a concentrate of VWF, characterised by preparation of a solution of VWF and nanofiltration of the solution through a filter having a pore size of 20 nanometers,

at a maximum pressure of less than or equal to 0.5 bar, in the presence of calcium ion and at a pH greater than 5.5.

7. The board furthermore notes in this context that it was undisputed between the parties that the first embodiment of claim 1 is directed to a process for nanofiltration, while the intended therapeutic use of VWF to treat von Willebrand Disease (VWD) is not a feature of claim 1.

Inventive step - claim 1

Closest prior art

8. The present invention is for obtaining a concentrate of VWF that can be used for the treatment of VWD (see paragraph [0001] of the patent). The opposition division considered the disclosure in document D8 to be the closest prior art. The parties accepted this finding on appeal for the first embodiment of claim 1, and the board sees no reason to differ.
9. Document D8 concerns the development of a human plasma-derived VWF concentrate that has high specific activity and is safe for the treatment of patients with VWD. It discloses the purification of VWF using filtration through filters with a pore size of 35 nm at a pressure of 200 ± 50 mbar, i.e. less than 0.5 bar, followed by dry heating (see abstract and page 102, left-hand column, first paragraph). Nanofiltration efficiently removed lipid-enveloped and non-enveloped viruses with a diameter larger than 35 nm while dry heating inactivated the hepatitis A virus and reduced the titre of porcine parvovirus, used as a model for human parvovirus B19 (see page 102, right-hand column, first

paragraph and table 1). Functional activity of the VWF concentrate was determined by measuring the ability of VWF to bind to platelets and FVIII *in vitro* (see page 102, left-hand column, second paragraph and page 103, paragraph bridging columns).

Technical problem and its solution

10. The process as defined in the first embodiment of claim 1 differs from the process disclosed in document D8 in that a 20 nm filter is used instead of a 35 nm filter and nanofiltration is carried out in the presence of calcium ions and at a pH of greater than 5.5.
11. The parties were in agreement - and the board sees no reason to differ - that the effect of using a 20 nm pore size filter is that more small non-enveloped viruses are removed from the VWF preparation than by filtration over a 35 nm filter (see paragraph [0001] of the patent in suit). The available prior art confirms that virus filters of 20 nm pore size remove small non-enveloped viruses such as the hepatitis A virus and B19 more effectively than a 35 nm pore size filter (see document D1, abstract, third paragraph and page 123, left-hand column, second paragraph).
12. The respondent did not dispute that, whereas the patent discloses that the FVIII/VWF complex dissociates in the presence of CaCl_2 in a concentration greater than 0.02 M (see paragraph [0020]), it is silent on a technical effect associated with the presence of calcium ions during the purification of uncomplexed VWF. Accordingly, the presence of calcium does not have any technical effect in the context of the first embodiment of the claimed invention and thus cannot contribute to

an inventive step within the meaning of Article 56 EPC (see Case Law of the Boards of Appeal, 2016, 8th edition, section I.D.9.1.2).

13. Paragraph [0036] of the patent discloses that a pH of greater than 5.5 is required "*to prevent denaturation*", albeit without specifying whether this concerns denaturation of VWF or of the FVIII/VWF complex. The board notes in this context that the VWF concentrate of document D8 has a high specific activity (see point 9 above), which indicates to the skilled person that it too is not denatured.
14. In view of the above considerations, the problem to be solved by the subject-matter of claim 1 vis-à-vis the disclosure of document D8 can thus be formulated as the provision of a process for obtaining a VWF concentrate having improved (virus) safety over the VWF concentrate disclosed in document D8. The board is satisfied that the problem is solved by the claimed subject-matter.

Obviousness

15. It needs to be established whether or not the skilled person, starting from the teaching in document D8 and faced with the objective technical problem (see point 14), would arrive at the claimed invention in an obvious manner.
16. Document D1 concerns the viral safety of FVIII, i.e. another plasma protein, and reports on the implementation of a nanofilter with a pore size of 20 nm in the manufacturing process to improve the viral safety of the FVIII product CROSS EIGHT M[®] (see abstract). In virus-spiking tests, filters of 20 nm were found to remove small non-enveloped viruses more

effectively than a 35 nm filter. Thus, while large viruses, such as pseudorabies virus and bovine viral diarrhoea virus, were completely removed by both 35 and 20 nm filters, small viruses, such as encephalomyocarditis virus, porcine parvovirus, the hepatitis A virus and human parvovirus B19, were removed only by the 20 nm filter, which thus markedly improves the viral safety of the FVIII product (see page 123, left-hand column, second paragraph and Table 3).

17. As regards the biochemical properties of FVIII, document D1 reports that "*no structural differences between the FVIII obtained after filtration with Planova 35N or Planova 20N*" were found (see page 123, left-hand column, third paragraph). Document D1 continues by stating that "*furthermore, the contents and multimeric structure of vWF, which forms a complex with FVIII and stabilises FVIII, were investigated using enzyme immunoassays and immunoblotting assays, respectively. As a result, the contents of vWF were similar to those usually found (0.007 - 0.015 U of vWF/U of FVIII:C), and no differences were observed in the multimeric structure (Fig. 4)*" (see paragraph bridging the columns on page 123). Figure 4 depicts an immunoblotting analysis of FVIII and VWF after filtration with a 20 nm and a 35 nm filter, respectively (see legend of Figure 4). The importance of this finding is also mentioned as follows in the discussion section of the article: "*in particular, it was important that the contents and composition of the vWF multimer were not affected by filtration through a 20-nm filter, because vWF may play a vital role in stabilizing FVIII*" (see page 124, right-hand column, last paragraph).

18. Thus, document D1 informs the skilled person not only that removing small non-enveloped viruses by filtration with a filter of a pore size of 20 nm is technically feasible (see point 16) but also that filtration with a filter of 20 nm yields VWF with a preserved multimeric structure (see point 17).

19. The respondent submitted that the skilled person seeking a solution to the objective technical problem would not turn to document D1, which was concerned with concentrates of FVIII, rather than of VWF. Relying on documents D16 and D26, it argued that the product obtained in document D1 was not suitable for treating VWD and also that the conformational changes of VWF mentioned in document D1 would have discouraged the skilled person from using a 20 nm filter to obtain a VWF product that was suitable for treating VWD. Furthermore, based on the disclosure in document D3, it argued that the skilled person would have expected that VWF could not be filtered using a filter smaller than 35 nm.
 - 19.1 The respondent is right in arguing that document D16 states that commercial FVIII concentrates, except those specifically prepared to retain all VWF forms, are of limited efficacy in treating VWD (see page 43, second paragraph) and that, according to document D26, the FVIII product of document D1 is not functional for the treatment of VWD (see Table 3). The board notes, however, that the skilled person would be aware that the process disclosed in document D1 is directed at the purification of FVIII, i.e. not of VWF, and comprises an immuno-affinity chromatography step with an anti-FVIII antibody (see page 120, right-hand column, first paragraph and Figure 1). The skilled person would also know that this purification step leads to a low content

in VWF in the FVIII product, thereby rendering it unsuitable for the treatment of VWD.

19.2 In the board's judgement, the fact that document D1 concerns a FVIII product and not a product that can be used to treat VWD would thus not have deterred the skilled person from considering its teaching as regards the removal of small non-enveloped viruses with a 20 nm filter from concentrates of a plasma protein (see point 16). Furthermore, the skilled person interested in VWF would have learned from Figure 4 of document D1 that the multimeric structure of VWF is the same in the 35 nm and the 20 nm filtrate. From document D8 the skilled person would already know that filtration over a 35 nm filter yields a product that is suitable for the treatment of VWD (see point 9). Accordingly, the board considers that the skilled person would have no reason to doubt that filtration over a 20 nm filter also yields a product that is suitable for the treatment of VWD. Finally, there is nothing in document D1 to indicate that the VWF is inactive after filtration through a 20 nm filter.

19.3 In relation to the mention in document D1 of conformational changes which might have made it possible for the FVIII/VWF complex to pass through the 20 nm pore size filter, the board refers to point 17, above, and notes that document D1 is silent on whether or not such conformational changes impair the activity of VWF.

19.4 The board notes that, whereas document D3 discloses that "*improvement in purity and low protein concentration have made nanofiltration of VWF solution on 35 nm membranes possible*" (page 31, left-hand column, third paragraph), it does not disclose that VWF

should only be filtered over a 35 nm filter or that it cannot be filtered over a filter with a smaller pore size, e.g. 20 nm. In any case, at the effective date of the first embodiment of claim 1, the skilled person would also have been aware of the teaching of document D1, which was published about three years after document D3, and thus of the fact that high molecular forms of VWF pass equally well through filters with a pore size of 20 nm as through filters with a pore size of 35 nm.

- 19.5 The respondent has also referred to document D2, which discloses that filtration over a filter having a pore size of 15 nm leads to a significant reduction in the percentage of the highest-molecular-weight (> 15 mer) VWF multimers (see abstract and page 332, right-hand column, second paragraph). In the board's judgement, however, this disclosure would not deter the skilled person from using a 20 nm filter, i.e. a filter with a larger pore size appearing to be suitable for the filtration of VWF in the light of the teaching of document D1 (see point 18).
- 19.6 To summarise, the board considers that the disclosure of document D1 would have motivated the skilled person faced with the objective technical problem of providing a process for obtaining a VWF concentrate having an improved virus safety to use a 20 nm filter instead of a 35 nm filter in the nanofiltration of a solution of VWF.
20. As regards the technical features "*at a maximum pressure of less than or equal to 0.5 bar, in the presence of calcium ion and at a pH greater than 5.5*" (see point 6), the board notes that document D8 discloses that the filtration of VWF was carried out by

applying a constant working nitrogen pressure of 200 ± 50 mbar (see page 102, left-hand column, first paragraph), whereas in document D1 it was found that the pressure could be varied between 0.2 and 0.8 kgf/cm² (i.e. between 196 and 784 mbar) without affecting the FVIII yield (see Table 1 and page 123, left-hand column, first paragraph).

21. In the board's judgement, the skilled person aware of these teachings would have considered that a pressure of 200 ± 50 mbar was a suitable option for the filtration of VWF, given that this was the pressure applied in document D8 for the filtration of VWF and that it also fell within the range employed in document D1 for the filtration of an even bigger molecule, the FVIII/VWF complex.
22. The board further considers that, in the absence of any explicit guidance in document D8 as regards the pH of the solution to be filtered, the skilled person would have turned to document D1 for guidance. This document discloses that the solution comprising the FVIII/VWF complex applied to the 20 nm filter contained 40 mM calcium chloride at pH 6.35 (see page 120, right-hand column, first paragraph and Figure 1). By applying these conditions to the VWF solution to be filtered the skilled person would arrive at the claimed process in an obvious manner.
23. In view of the above considerations the board concludes that the subject-matter of the first embodiment of claim 1 lacks inventive step (Article 56 EPC) and that the main request must be rejected.

Auxiliary request I

Inventive step - claim 1

24. One of the differences between the subject-matter of claim 1 of this request and that of claim 1 of the main request is that the process is for the production of a VWF filtrate that is now explicitly defined as suitable for the treatment of VWD (see section VIII).

Closest prior art, technical problem and its solution

25. In the board's judgement, for the subject-matter of this claim 1 too, document D8 is the closest prior art. The problem this subject-matter is designed to solve vis-à-vis the disclosure in that document can be formulated as the provision of a process for obtaining a VWF concentrate with improved (virus) safety that is suitable for the treatment of VWD. The board is satisfied that the problem is solved by the claimed subject-matter.

Obviousness

26. The respondent maintained that the skilled person would not consult document D1 and would have no reasonable expectation that filtration through a 20 nm filter would successfully result in a product that was suitable for the treatment of VWD (see section X).
27. However, in the board's judgement, the skilled person faced with the objective technical problem would have turned to document D1 for the same reasons as set out above in the context of the main request. In brief, document D1 informs the skilled person not only that removing small non-enveloped viruses by filtration with

a filter of a pore size of 20 nm is technically feasible (see point 17) but also that filtration over a 20 nm filter yields VWF with the same multimeric structure as filtration over 35 nm filter. The skilled person would consider this product to be suitable for the treatment of VWD (see points 17 and 19.2).

28. Therefore, in the board's judgement, the skilled person would have had no reason to adopt a sceptical attitude. Moreover, to find out whether VWF is indeed suitable for the treatment of VWD after filtration through a 20 nm filter, it suffices to perform well-known, routinely carried-out *in vitro* tests such as those disclosed in document D8 (see point 9 above). In doing so the skilled person would have had either some expectation of success or, at worst, no particular expectations of any sort but only a try-and-see attitude, which does not, however, equate to an absence of a reasonable expectation of success (see decision T 91/98 of 29 May 2001, reasons, point 8 and decision T 1045/98 of 22 October 2001, reasons, point 17).
29. In view of the above considerations the board concludes that the subject-matter of claim 1 of auxiliary request I lacks inventive step (Article 56 EPC).

Auxiliary request II

Admission into the appeal proceedings

30. This claim request was filed during the oral proceedings, after the board had stated its opinion that the subject-matter of claim 1 of auxiliary request I did not comply with the requirements of Article 56 EPC.

31. Claim 1 of auxiliary request II differs from claim 1 of auxiliary request I in that the first embodiment relating to VWF has been deleted (see section VIII). It amounts to an amendment to the respondent's case and its admission is thus at the board's discretion (Article 13 RPBA).
32. The respondent submitted that the request should be admitted into the appeal proceedings because it addressed an objection discussed during the oral proceedings by limiting the subject-matter of claim 1 to the second embodiment. It conceded that the request had been filed late but argued that the focus of the debate had shifted from the second embodiment of claim 1 to the first embodiment.
33. The board notes, however, that both appellants had raised objections that the first embodiment of claim 1 lacked inventive step, based on a combination of the disclosure in document D8, the closest prior art and document D1, in their statements of grounds of appeal (see section V above). Furthermore, the respondent was already aware prior to the oral proceedings that the board agreed with the construction the opposition division had given claim 1 in the decision under appeal (see section VII).
34. The board concedes that the fact that the debate in the oral proceedings focused on inventive step of the first embodiment of claim 1, present in all claim requests on file prior to the oral proceedings, might, subjectively, have come as a surprise to the respondent. Objectively, however, it does not qualify as an unforeseeable development in the proceedings that would justify admitting amended claims submitted for the first time during the oral proceedings, when the

objection thereby addressed has been in the appeal proceedings from the beginning. Moreover, that the board found against the respondent in the oral proceedings does not as such justify admitting a claim request which could - and, when taking the circumstances of the case into account, should - have been filed earlier.

35. The appellants and the board prepared the case on the basis of the claim requests on file prior to the oral proceedings. None of these claim requests was limited to the second embodiment of claim 1.
36. It was also not immediately apparent to the board that the new claim request was clearly and obviously allowable.
37. Given the circumstances of the present case, the board considered that not even the fact that the claim request had been filed in the afternoon of the first of the two days scheduled for oral proceedings, i.e. at a point in time when more than one day was still remaining, could tip the balance in the respondent's favour. As a general rule, oral proceedings are scheduled with the aim of ensuring that a final decision can be taken at the end of the oral proceedings in accordance with Article 15(6) RPBA and, hence, on the assumption that all relevant issues will be addressed at the oral proceedings. In the present case it should be borne in mind that the board started the discussion at the oral proceedings with the topic of inventive step and a number of other issues had not yet been addressed at all, meaning there was a risk that the remaining time might not have been sufficient to terminate the appeal case without infringing the

parties' right to fair proceedings.

38. Therefore, the board decided not to admit auxiliary request II into the appeal proceedings because it was late-filed, it could have been filed earlier and admitting the request into the proceedings at this stage would have run counter to the need for procedural economy and to the principle of procedural fairness (Articles 13(1) and (3) RPBA).

Auxiliary requests III to VII

Inventive step - claim 1

39. While claim 1 of each of these requests has been amended with respect to claim 1 of the main request (see section VIII), no argument was submitted by the respondent why any of these amendments rendered the claimed subject-matter inventive over the combination of the teaching of document D8 with the disclosure of document D1.
40. The board considers that the subject-matter of claim 1 of auxiliary requests III to VI relates to, *inter alia*, the nanofiltration of a solution containing only VWF and thus corresponds to the first embodiment of claim 1 of the main request. Claim 1 of auxiliary request VII additionally requires that the filtrate be suitable for the treatment of VWD.
41. The reasoning set out above for claim 1 of the main request (see points 8 to 23) thus applies *mutatis mutandis* also to the subject-matter of claim 1 of auxiliary requests III to VI, while the reasoning set out above for claim 1 of auxiliary request I (see points 24 to 29) applies *mutatis mutandis* to the

subject-matter of claim 1 of auxiliary request VII.
This has not been contested by the respondent.

42. Therefore, the subject-matter of auxiliary requests III to VII also lacks inventive step (Article 56 EPC).

Conclusion

43. The board concludes that none of the claim requests considered by it meets the requirements of Article 56 EPC. Accordingly, the patent cannot be maintained on the basis of any of these claim requests and, in the absence of any other, allowable claim request in these proceedings, must be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



N. Schneider

B. Claes

Decision electronically authenticated