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Datasheet for the decision of 28 June 2016

Case Number: T 0587/12 - 3.3.04

Application Number: 07380021.1

Publication Number: 1820509

IPC: A61K38/36, A61P7/04

Language of the proceedings: EN

Title of invention:
Therapeutic preparation of very high purity FVIIa and method for obtaining same

Patent Proprietor:
Grifols, S.A.

Opponent:
CSL Behring GmbH

Headword:
Factor VIIa/GRIFOLS

Relevant legal provisions:
EPC Art. 108, 54(2), 56
EPC R. 99(2), 115(2)
RPBA Art. 12(4), 15(3)

Keyword:
Scope of appeal
Main request - novelty, inventive step (yes)

Decisions cited:
T 0220/83

Catchword:

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Case Number: T 0587/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 28 June 2016

Appellant: (Opponent)	CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg (DE)
Representative:	Peter, Beate CSL Behring GmbH Patents & Licenses Emil-von-Behring-Strasse 76 35041 Marburg (DE)
Respondent: (Patent Proprietor)	Grifols, S.A. C/Jesús y María, 6 08022 Barcelona (ES)
Representative:	Zimmer, Franz-Josef Grünecker Leopoldstr. 4 80802 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 January 2012 rejecting the opposition filed against European patent No. 1820509 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	B. Claes
Members:	R. Morawetz
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal of the opponent ("appellant") lies against the decision of the opposition division rejecting the opposition filed against European patent No. 1820509.

II. The patent at issue has the title "*Therapeutic preparation of very high purity FVIIa and method for obtaining same*". It was granted in respect of European patent application No. 07380021.1.

Claim 13 as granted read:

"13. A therapeutic preparation of FVIIa obtained by a method according to anyone of claims 1 to 12, **characterized in that** its purity is at least 1000 IU/mg of protein." (emphasis in the original).

Claims 14 to 17 as granted are dependent on claim 13.

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

D9 Tomokiyo K. *et al.*, Vox Sanguinis (2003), vol. 84, pages 54 to 64.

D10 Van Deijk W.A. *et al.*, Haemostasis (1983), vol. 13, pages 192 to 197.

D11 Orthner C.L. *et al.*, Vox Sang (1995), vol. 69, pages 309 to 318.

D12 US4,479,938

D13 EP 0 346 241 A1

D14 Marks J.D. *et al.*, J.Mol.Biol (1991), vol. 222, pages 581 to 597.

D15 WO 98/24893

D16 Grandics P. *et al.*, Annals of the New York Academy of Sciences, Biochemical Engineering (1990), vol. 589, pages 148 to 156.

D17 Beer D.J. *et al.*, Journal of Immunological Methods (1994), vol. 173, pages 103 to 109.

D18 Chames P. *et al.*, British Journal of Pharmacology (2009), vol. 157, pages 220 to 233.

D19 Sommerfeld S. and J. Strube, Chemical Engineering and Processing (2005), vol. 44, pages 1123 to 1137.

D20 ICH Harmonised Tripartite Guidelines, Current Step 4 version, 10 March 1999, pages 1 to 16.

IV. In the decision under appeal the opposition division held *inter alia* that the disclosure of document D2 did not anticipate the subject-matter of claims 13 to 17 as granted because "*it is not clearly and unambiguously derivable from D2 that the unit U/mg given for the specific activity of FVIIa in D2 is identical or comparable to standard IU/mg in the patent in suit. Furthermore, D2 does not disclose purification starting from Cohn fractions II + III, or III, or equivalent of Cohn fractioning involving a PEG precipitation step. Since cryoprecipitate was used as starting material and a PEG precipitation not comprised in the purification it cannot be excluded that the end product has a different composition in background proteins than in*

the patent in suit. Thus the chemical composition of the products in D2 and the contested patent are not identical" (see decision under appeal, reasons, point 2.2.1).

As regards inventive step of the subject-matter of claims 1 to 12 taking document D2 to represent the closest prior art, the opposition division was of the view "*that the solution does not appear obvious because there is no indication or suggestion in D2 to add a PEG precipitation. Even if the SKP would have been motivated to add an additional purification step, there is no pointer to specifically choose PEG precipitation as many alternatives exist in the prior art (such as e.g. salting out). The combination of D2 with D6 or D5 can therefore only be arrived at with ex post facto analysis*" (*ibid.*, point 2.4.1).

As regards the disclosure in document D1 and inventive step of claims 13 to 17 as granted, the opposition division held that "*Dl neither discloses a method of preparation of FVIIa nor is directed to plasma derived FVIIa. There are too many differences between Dl and the patent in suit in order for the SKP to consider Dl as a starting point for a problem solution approach and to combine it with D4. The same applies to a combination of Dl with D7*" (*ibid.*, point 2.4.1).

Lastly, as regards sufficiency of disclosure the opposition division held that "*the patent in suit discloses in paragraphs 14-26 specific procedural steps and parameters to obtain FVIIa with an activity of at least 1000 IU/mg from given starting materials. Furthermore, an exemplary embodiment describing consecutive stages of the purification is disclosed (see column 4, Example)*" and as regards calibration to

international units "*the patent in suit discloses in column 7, lines 3-7 that the analytical evaluations of the samples for the activity of FVIIa were carried out with a test assay kit to the 1st International FVIIa standard*" (*ibid.*, point 2.3.1).

V. With its statement of grounds of appeal the appellant filed documents D11 to D15.

VI. With its response to the statement of grounds of appeal the respondent filed documents D16 to D19.

VII. The parties were summoned to oral proceedings and subsequently informed of the board's preliminary opinion in a communication according to Article 15(1) RPBA. In particular, the board indicated that it considered that the appeal proceedings were "*limited to the issue of novelty of the subject-matter of claims 13 to 17 vis-à-vis document D9 - and possibly documents D13 and D14 - and the issue of inventive step of the subject-matter of claims 13 to 17 vis-à-vis document D9*".

VIII. In preparation of the oral proceedings the respondent filed further arguments and document D20.

IX. Although the appellant had announced by letter dated 30 May 2016 that it intended to attend the oral proceedings, it was neither present nor represented at them. After several unsuccessful attempts by the board to reach the appellant's representative, the board decided, in accordance with Rule 115(2) EPC and Article 15(3) RPBA, to conduct the oral proceedings without this party. At the end of the oral proceedings the chairman announced the board's decision.

X. The arguments of the appellant submitted in writing and relevant for the present decision may be summarised as follows:

Novelty

Document D9 provided an industrial process for the provision of factor VII which started from cryopoor human plasma and provided a FVIIa preparation with a specific activity of about 40000 IU/mg.

The authors of document D9 observed no murine antibody in the final preparation on conducting a very sensitive enzyme-linked immunosorbent assay (ELISA) test. They dealt with the problem of leakage of mouse IgG by using a DEAE Fast Flow (DEAE-FF) chromatography to quantitatively remove any potentially leaked mouse IgG.

Document D11 corresponded to reference [16] in document D9 and described the ELISA used for the detection of mouse IgG. This ELISA would have detected fragments of mouse antibody as well, as it used polyclonal anti-mouse IgG for capturing and detection and thus recognised epitopes distributed throughout the IgG molecule.

Inventive step

The disclosure in document D9 could be considered to represent the closest prior art for the subject-matter of claim 13 as granted. The only difference between the claimed invention and the preparation disclosed in document D9 was that it could not be excluded that non-human protein, *i.e.* mouse antibody or fragments thereof, might be present in the factor VIIa preparation. The skilled person "faced with this

difference" would have easily had the means to prepare human monoclonal antibodies to FVII and to replace the affinity chromatography step using a mouse monoclonal antibody with an affinity chromatography step using an equivalent human monoclonal antibody, or at least a chimeric or humanised antibody.

Several approaches for preparing human monoclonal antibodies were available before the priority date of the patent, see e.g. documents D14 and D15.

XI. The arguments of the respondent relevant for the present decision may be summarised as follows:

Substantiation of the appellant's appeal (Article 108 EPC and Rule 99(2) EPC)

The appellant had failed to submit substantiated arguments as to why the decision of the opposition division taken in view of documents other than document D9 was incorrect. Thus, the grounds of appeal did not present substantiated facts, arguments nor evidence as regards the opposition division's finding that the subject-matter of claims 13 to 17 as granted was novel over the disclosure in document D2; that the patent sufficiently disclosed the claimed invention; and that the subject-matter of claims 1 to 12 was based on an inventive step in view of the disclosure in document D2, and that the subject-matter of claims 13 to 17 as granted was based on an inventive step in view of the disclosure in document D1 in combination with the teaching of document D4 or D7.

Scope of the appeal proceedings

The appeal was limited to objections to claims 13 to 17 as granted based on document D9 and in as far as they related to novelty and inventive step.

Novelty

Document D9 reported that murine antibody was not detected but it did not look for fragments.

It had to be assumed that antibody-derived fragments were present in the preparation of document D9, which fragments stemmed from the mouse IgG used for immunopurification, which typically occurred when a chromatography column was employed and which were not detectable using the ELISA format of document D9.

The ELISA used in document D9 was a modified version of the ELISA of document D11, but the nature of the modification was not known. Moreover, document D11 was silent on whether or not the ELISA was suitable for detecting any type of IgG fragments leaching from the immunoadsorption purification into the final product. The ELISA tested only for a particular region of the antibody used in the immunopurification, namely the region specific for its classification as IgG. According to document D11 the calibration of the ELISA used the complete purified IgG antibody Mab8861. There was thus no hint that the antibody used in document D9, let alone fragments thereof, could be detected by the ELISA.

Claims 13 to 17 as granted were limited to therapeutic preparations free of proteins of non-human origin and thus novel.

Admissibility of document D12 and D13

The objections based on these two new documents were very poorly substantiated. The activity units for the characterisation of factor VIIa used in these documents were different to the one used in claim 13 as granted. The issue of the activity units had already been addressed in the opposition proceedings. The documents should be held inadmissible.

Inventive step

The contamination of the therapeutic preparation with proteins of non-human origin led to antigenic reactions in the patients treated with these preparations (see paragraph [0011] of the patent in suit). It was an objective of the invention to avoid the immune response caused by contamination by non-human proteins present in factor VIIa preparations.

The argument of the appellant was based on hindsight. The skilled person would not use human monoclonal antibodies to purify the preparation of document D9. In fact, human monoclonal antibodies against FVII/FVIIa were not available in the prior art and it was unpredictable whether such antibodies could be prepared with enough affinity to use them as immunoaffinity tools.

At the filing date of the present patent the skilled person would not have modified the teaching of document D9 by employing human monoclonal antibodies in order to overcome the contamination problems arising from the use of monoclonal murine antibodies in the purification method of document D9.

XII. The appellant requested in writing that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. Although duly summoned, the appellant was neither present nor represented at the oral proceedings. The board considered it expedient to conduct the scheduled oral proceedings in the appellant's absence in order to reach a final decision in this appeal case. The appellant was treated as relying on its written case in accordance with Rule 115(2) EPC and Article 15(3) RPBA.

Substantiation of the appellant's appeal (Article 108 EPC and Rule 99(2) EPC)

2. Article 108 EPC, third sentence, in conjunction with Rule 99(2) EPC stipulates that in the statement of grounds of appeal the appellant must indicate the reasons for setting aside the decision impugned, or the extent to which it is to be amended, and the facts and evidence on which the appeal is based. In line with established jurisprudence of the Boards of Appeal this is understood to mean that the arguments have to be clearly and concisely presented to enable the board - and any other party or parties - to understand immediately why the impugned decision is alleged to be incorrect, and on what facts the appellant bases its arguments, without first having to make investigations of their own (Case Law of the Boards of Appeal, 7th edition 2013, section IV.E.2.6.3 and decision T 220/83,

OJ EPO 1986, 249).

3. In the present case, the impugned decision held that the subject-matter of claims 13 to 17 as granted was novel *vis-à-vis* the disclosure in documents D2 and D9; that the subject-matter of claims 1 to 12 as granted was inventive over the disclosure in document D2 in combination with the disclosure in document D5 or D6; that the subject-matter of claims 13 to 17 as granted was inventive over the disclosure in document D9 in combination with the common general knowledge and over the disclosure in document D1 in combination with the teachings in documents D4 or D7; and that the patent sufficiently disclosed the claimed invention.

4. The appellant submitted in the statement of grounds of appeal the following:

4.1 Under the heading "*Grounds for Appeal*", that "*We maintain our arguments already provided during the Opposition procedure. We request revocation of the patent, on the grounds of lack of novelty, lack of inventive step, and insufficiency (Art. 100(a) and (b), Art. 54, 56 and 83 EPC). The objections have been put forward in detail in the opposition and further documents filed during the opposition procedure, which we maintain, but will not repeat in detail here.*"

4.2 Under the heading "*Novelty*", that "*we maintain the objections put forward during the opposition procedure. In addition, we would like to further substantiate the objections based on document D9 against claims 13 to 17 here*". The appellant also submitted new documents D12 and D13 and based objections as regards lack of novelty on these new documents (see also below, points 16 to

21).

4.3 Under the heading "*Inventive step*", that document D9 could be considered to represent the closest prior art for the subject-matter of claims 13 to 17 as granted. The appellant based its arguments on the disclosure in document D9 in combination with the teachings in newly filed documents D14 and D15.

4.4 No arguments were submitted to substantiate the objection of lack of sufficiency of disclosure.

5. The appellant's argumentation (see points 4.1 to 4.4 above) in relation to the reasons given in the decision under appeal (see section IV) for finding that document D2 does not anticipate the subject-matter of claims 13 to 17 as granted does not fulfil the criterion set out in point 2 above. It neither explains why the opposition division's reasoning was incorrect, nor is this self-evident by implication. The same applies for the opposition division's decision as regards inventive step of claims 1 to 12 as granted over the disclosure in document D2, inventive step of claims 13 to 17 as granted over the disclosure in document D1, and sufficiency of disclosure (see points 4.1 to 4.4 above).

6. However, the board considers that the arguments provided by the appellant as regards novelty and inventive step of the subject-matter of claims 13 to 17 as granted *vis-à-vis* the disclosure in document D9 enable the board and the respondent to understand why it regarded the contested decision as incorrect on those points.

Scope of the appeal proceedings

7. In view of its considerations above regarding substantiation of the appellant's appeal, the board decided that the appeal proceedings were limited to the issues of novelty and inventive step of the subject-matter of claims 13 to 17 as granted *vis-à-vis* the disclosure in document D9.

Novelty - claims 13 to 17 as granted

8. The subject-matter of claim 13 as granted relates to a therapeutic preparation of activated factor VII (FVIIa) which is characterised in terms of the process of its production and a purity of at least 1000 IU/mg of protein (see section II). The opposition division held that as a consequence of the process feature, the FVIIa preparation of claim 13 was free of proteins of non-human origin. This was not contested by the appellant.

9. Document D9 describes the large-scale production of human plasma-derived FVIIa (see abstract). FVII is purified from human cryoprecipitate-poor plasma by a combination of anion exchange and immunoaffinity chromatography, using an anti-FVII monoclonal antibody (anti-FVIImAb). To activate FVII, the FVII preparation is partly converted to FVIIa by autoactivation on an ion-exchange resin, and the specific activity of the purified FVIIa preparation is 40000 U/mg. Document D9 reports that leakage of anti-FVIImAb, a mouse IgG, in the FVIIa preparation from the immunoaffinity resin can be removed by DEAE-FF chromatography to the pass-through fraction and that mouse IgG was not detected by ELISA in the eluate of DEAE-FF or in the FVIIa concentrate (see page 63, right hand column, first

paragraph and Table 2).

10. The opposition division held that it could not be excluded that monoclonal antibodies immobilised on the immunoaffinity column were fragmented by enzymes present in the plasma from which the FVII was purified and that the resulting fragments might not contain the epitope recognised in the ELISA used for the detection of mouse IgG in document D9. Accordingly, it held that the absence of non-human proteins in the product of document D9 had not been proven.

11. The appellant has not disputed that fragmentation of the immobilised mouse antibody occurred, but it submitted that the ELISA used in document D9 would have detected fragments of the mouse antibody used for immunopurification of FVII as well, because the anti-mouse IgG antibodies used in the ELISA recognised, thanks to their polyclonal nature, epitopes distributed throughout the IgG molecule.

12. The board is not persuaded by this line of reasoning. The board notes that although document D9 states that: "*Anti-FVII mAb was quantified by sandwich ELISA for murine IgG, using a modification of a previously described procedure [16]. The limit of detection for anti-FVII mAb was 0-25 ng/ml*." (see page 56, left hand column, first paragraph), it is silent on the type of antibody used in the ELISA, *i.e.* whether it was monoclonal or polyclonal. Moreover, document D9 does not mention the possible detection of antibody fragments. The type of modification vis-à-vis the ELISA described in reference [16] is also not explained.

13. Reference [16] cited in document D9 is document D11 in the present appeal proceedings and describes a sandwich

ELISA for murine IgG in which microtiter plates were coated with goat anti-murine IgG and captured IgG was detected with goat anti-murine IgG conjugated to alkaline phosphatase (see page 311, right hand column, sixth paragraph). The ELISA described in document D11 thus only tests for that region of the antibody specific for its classification as IgG. However, document D11 too is silent on the detection of antibody fragments or whether the antibody used was polyclonal or monoclonal.

14. Thus, neither document D9 nor document D11 discloses whether the antibodies used for capture and detection in the disclosed ELISA were polyclonal or monoclonal. The appellant's submission that the ELISA would have detected fragments of mouse antibody as well, as it used polyclonal anti-mouse IgG for capture and detection and would thus necessarily have recognised epitopes distributed throughout the IgG molecule, thus appears unsupported by the evidence on file. The appellant's argument that the authors of document D9 have shown beyond reasonable doubt that no murine antibody or fragments thereof are present in the final preparation must therefore fail.

15. In view of the above considerations the board concludes that the subject-matter of claim 13, and of its dependent claims 14 to 17, is not anticipated by document D9. This subject-matter is therefore new.

Documents D12 and D13

16. Article 12(2) RPBA stipulates that the statement of grounds of appeal must set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld, and should

specify expressly all the facts, arguments and evidence relied on. According to Article 12(4) RPBA the board can hold inadmissible evidence which does not fulfil the requirements of Article 12(2) RPBA.

17. The appellant filed documents D12 and D13 with its statement of grounds of appeal and submitted that they anticipated the subject-matter of claim 13 as granted.

18. The sole passage of document D12 referred to by the appellant discloses a purified factor VII which "*prior to activation contained 3,250 units of factor VII/mg protein*". The activity was determined according to the method of Nemerson and Clyne (see column 8, lines 12 to 18). The sole passage of document D13 referred to by the appellant discloses a preparation comprising FVII with an activity of 2500 U/ml and a protein concentration of 2 to 4 g/l (see column 6, lines 16 to 25).

19. The board notes that the activities of the FVII preparations of documents D12 and D13 are not given in IU/mg of protein. The appellant has provided no argumentation as to why the activity values of the FVII preparations disclosed in documents D12 and D13 fall within the scope of claim 13 as granted, which defines the activity of FVIIa in terms of IU/mg of protein, and nor is this self-explanatory.

20. The appellant has also failed to provide any arguments as to why the preparations of document D12 and D13 fulfil the other criteria of claim 13 as granted, in particular the requirement that non-human proteins be absent. This is also not apparent from the sole passages of documents D12 and D13 referred to by the

appellant.

21. The appellant's submissions with regard to documents D12 and D13 do not enable the board to understand immediately and without further investigations why it takes the view that they anticipate the subject-matter of claim 13 as granted. Therefore, the board considered that those submissions failed the requirements of Article 12(2) RPBA and decided to hold documents D12 and D13 inadmissible under Article 12(4) RPBA.

Inventive step (Article 56 EPC)

Closest prior art

22. The present invention pertains to the provision of a therapeutic preparation of high-purity FVIIa. The parties agreed that document D9 represents the closest prior art and the board sees no reason to differ.

23. The therapeutic preparation of FVIIa defined in claim 13 as granted differs from the preparation disclosed in document D9 (see point 14) in that it is free from proteins of non-human origin. The effect associated with this difference is avoidance of antigenic reactions in patients treated with the preparation (see paragraph [0011] of the patent in suit).

The technical problem to be solved

24. In the board's judgement, starting from the disclosure in document D9 the technical problem to be solved is the provision of a therapeutic preparation of FVIIa which does not lead to antigenic reactions in the patients treated with it. The board is satisfied that

the subject-matter of claim 13 as granted solves this technical problem.

Obviousness

25. The relevant question in the context of obviousness is whether the skilled person, faced with the technical problem defined above, would have modified the teaching of the closest prior art document so as to arrive at the claimed invention in an obvious manner.

26. The appellant submitted that the skilled person had the means to prepare human monoclonal antibodies to FVII and to replace the affinity chromatography step using a mouse monoclonal antibody described in document D9 with an affinity chromatography step using an equivalent human monoclonal antibody. It relied on documents D14 and D15 to show that approaches for preparing human monoclonal antibodies were available well before the priority date of the patent in suit.

27. The board notes that document D9 itself is silent on the possible use of human monoclonal antibodies in the affinity chromatography step, although the authors were certainly aware of the problem of mouse antibody leakage into the FVII preparation from the immunoaffinity column and the ensuing contamination of the therapeutic preparation (see page 63, right hand column, first paragraph). Moreover, there is no evidence on file to the effect that at the priority date of the patent in suit a human monoclonal antibody against FVII was available in the art. The available prior art neither refers to human anti-FVII monoclonal antibodies nor indicates that it was possible to obtain them with sufficient affinity to use them as immunoaffinity tools for the purification of FVII

therapeutic proteins.

28. In the board's judgement, the mere assertion that human monoclonal antibodies against FVII could have been made by the skilled person does not begin to explain why the skilled person would have made and used them in the process of document D9 in the absence, in the art, of any motivation to do so in the first place. The board concludes that at the filing date of the patent in suit the prior art provided no incentive to the skilled person to modify the teaching of document D9 by employing human monoclonal antibodies in order to overcome the contamination problems arising from the use of monoclonal murine antibodies in the purification method of document D9.

29. The skilled person would thus not have arrived in an obvious manner at the subject-matter of claim 13 as granted. Dependent claims 14 to 17 as granted derive their inventive step from the subject-matter of claim 13 as granted. The main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Cremona B. Claes

Decision electronically authenticated