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Datasheet for the decision of 28 February 2019

Case Number: T 0287/15 - 3.3.01

Application Number: 05380229.4

Publication Number: 1649867

IPC: A61K38/48, A61K47/48, A61K9/19, C12N9/74

Language of the proceedings: EN

Title of invention:
Stable thrombin composition

Applicant:
Grifols, S.A.

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:
Amendments - added subject-matter (no)
Inventive step - (yes)

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Case Number: T 0287/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 28 February 2019

Appellant: (Applicant)	Grifols, S.A. C/Jesús y María, 6 08022 Barcelona (ES)
Representative:	Durán Moya, Luis-Alfonso DURAN-CORRETJER Còrsega, 329 (Paseo de Gracia/Diagonal) 08037 Barcelona (ES)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 August 2014 refusing European patent application No. 05380229.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	P. de Heij

Summary of Facts and Submissions

I. The decision under appeal is the decision of the examining division refusing European patent application No. 05 380 229.4.

II. The documents cited in the course of the examination and appeal proceedings include the following:

D1: WO 99/23111 A1

D2: US 5 506 127 A

D6: BIOSIS accession no. PREV200100147421 &
Biol Pharm Bull 23(2), 1406-1409 (2000)

III. In the decision under appeal, which was based on a main request and two auxiliary requests, the examining division found that the subject-matter of claim 1 of the main request lacked novelty (Articles 52(1) and 54 EPC). The subject-matter of the claims of the first auxiliary request did not involve an inventive step starting from the technical teaching of document D2, in combination with the teaching of document D6 (Articles 52(1) and 56 EPC). The second auxiliary request contained subject-matter extending beyond the content of the application as filed (Article 123(2) EPC).

IV. The applicant (appellant) filed an appeal against that decision, maintained the main request and the first auxiliary request, and submitted new sets of amended claims as its second to fourth auxiliary requests.

V. Oral proceedings before the board took place on 28 February 2019. During the oral proceedings, the appellant submitted the following set of claims 1 to 6 and withdrew all other pending requests:

*"**1.** The process for the preparation of a thrombin composition comprising purified thrombin,*

wherein the thrombin is purified to a specific activity of 1500 IU of thrombin/mg of protein or more and a strength of 500 IU of thrombin/ml or more,

stabilising the solution through adding and mixing with human albumin and a neutral salt, which is sodium chloride, wherein the concentration of human albumin in the thrombin composition prior to nanofiltration is between 0.05 and 1% w/v and the concentration of sodium chloride in the thrombin composition prior nanofiltration is at least 0.05 molar and at a pH between 5.0 and 8.5,

subsequently applying a double nanofiltration in series through filters of a nominal pore size of 15 nm to the solution, wherein the thrombin composition is nanofiltered with a good productivity of more than 15 Million IU thrombin per m^2 with a thrombin recovery of more than 90%;

wherein the nanofiltered material is not subsequently treated for adjustment of the composition, thereby avoiding any risk of cross-contamination.

***2.** The process according to claim 1, wherein the human albumin has a concentration prior to nanofiltration between 0.1% and 1% w/v.*

***3.** The process according to any of claims 1 to 2, wherein the composition is subjected to a freezing process.*

***4.** The process according to any of claims 1 to 3, wherein the composition is subjected to lyophilization.*

***5.** The process according to claim 4, wherein the lyophilized product is dry heat treated for a time of between 30 minutes and 8 hours at a temperature of between 90°C and 115°C.*

***6.** The process according to claim 5, wherein the lyophilized thrombin composition is dry heat treated for a time of 1-2 hours at 100°C."*

VI. The appellant's arguments concerning inventive step, as far as relevant to the outcome of the present decision, may be summarised as follows:

Document D2, which related to the preparation of stabilised and substantially virion-free therapeutic-grade thrombin compositions, was a suitable starting point for the assessment of inventive step. According to the skilled person's knowledge at the time when the application was drafted, at least two virus elimination stages supplementing each other in their effects were required in order to achieve an acceptable reduction in viral load. Accordingly, the process disclosed in example 2 of document D2 included, for the purpose of virus removal, a treatment with a solvent/detergent ("SD") composition for inactivating lipid-containing viruses and a step of nanofiltration. The process according to claim 1 differed from that in requiring, as the sole mandatory step for virus removal, double nanofiltration in series through filters having a pore size of 15 nm. The viability of the process was shown in example 1 of the application. The objective technical problem could thus be defined as the provision of a simplified process for preparing a thrombin composition with high viral safety. Neither document D2 itself nor documents D1 or D6 contained a pointer for the person skilled in the art to consider double nanofiltration as the solution to the technical problem.

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the sole pending request, submitted in the oral proceedings on 28 February 2019.

Reasons for the Decision

1. Admissibility of the appeal

The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC and is therefore admissible.

2. Amendments (Article 123(2) EPC)

2.1 Claims 1 and 2 find support in independent claim 14 of the application as filed combined with the passages on page 3, lines 18 to 27; page 4, lines 11 to 15; and page 4, line 25 to page 5, line 3 of the description.

2.2 Support for the additional technical features according to dependent claims 3 to 6 is provided on page 5, lines 25 to 29 of the description as filed.

2.3 As a consequence, the board has no objection to the present claims pursuant to Article 123(2) EPC.

3. Inventive step (Articles 52(1) and 56 EPC)

Application

3.1 European patent application No. 05 380 229.4 seeks to prepare a thrombin composition suitable for therapeutic use as a component of fibrin adhesives or for other haemostatic uses (see page 1, paragraph 1 of the description as filed). At the time of drafting, it was known that thrombin solutions must be adequately stabilised to prevent a loss of thrombin activity. Furthermore, as a product of biological origin, thrombin must be subjected to specific measures effective in eliminating pathogenic agents such as virus particles (see page 1, penultimate paragraph and the paragraph bridging pages 1 and 2).

3.2 The process defined in claim 1 of the appellant's sole pending claim request involves a purified thrombin composition which contains albumin for stabilisation (see page 3, last paragraph of the description) and which, for virus removal, is filtered through two filters with a nominal pore size of 15 nm which are arranged in series.

Starting point in the prior art

3.3 It was common ground that document D2, which relates to the preparation of stabilised and substantially virion-free therapeutic-grade thrombin compositions, was a suitable starting point in the prior art for the assessment of inventive step.

3.4 The process of preparation described in document D2 includes the incubation of crude thrombin starting material with a viricidal solvent/detergent ("SD") composition to inactivate lipid-containing enveloped virions, sequential ion-exchange chromatography with recovery of a final eluate containing purified thrombin, exchange of the chromatography buffer medium for a formulation medium in the form of a saline buffer solution comprising albumin as a stabiliser, and filtration of the thrombin formulation over a viral filter to remove non-lipid-containing virions (see D2: column 2, lines 45 to 67 and example 2 in column 8, line 40 to column 9, line 34). According to example 2 and the general disclosure in column 7, lines 25 to 36 of document D2, the nanofilter employed for that purpose has a pore size of 15 nm. As in the present application (see claims 5 and 6), optional dry-heat treatment after lyophilisation may follow to ensure the inactivation of any potentially remaining infective viral material.

3.5 Document D1 relates to processes for preparing components for forming fibrin glue from a pool of human plasma and, *inter alia*, discloses a process for preparing a thrombin formulation which comprises the same steps as the process according to document D2 (see D1: claim 26 and page 19, paragraph 2 making reference to document D2). Since the teaching of document D1 does not go beyond that of D2 with respect to virus removal, the board considers that D1 is not more promising than D2 as a starting point for the assessment of inventive step.

Technical problem and solution

3.6 The process as defined in claim 1 differs from the process according to D2 in the mandatory requirement for double nanofiltration in series through filters of a nominal pore size of 15 nm, meaning that a second nanofiltration is carried out in series, involving a filter of the same low pore size. SD treatment, on the other hand, is not mandatory.

3.7 It is mentioned in the application (see page 2, last paragraph) that filtration through 15 nm filters can guarantee a significant reduction in small naked viruses such as Hepatitis A virus and Parvovirus, which lie between 20 and 30 nm. The possibility of carrying out filtration in series using two 15 nm filters would increase the level of reduction in viral load and thus the level of safety with regard to these viruses. If this nanofiltration is carried out in a final stage, which avoids subsequent concentration operations and adjustment in the composition of the solution, it cancels out the possibility of accidental contamination of the nanofilter product. It is furthermore mentioned (see page 3, lines 18 to 23 of the description) that even the smallest viruses, such as monodispersed

Porcine Parvovirus, are retained to a level of more than log 4 (base 10).

3.8 The viability of the double nanofiltration step involving two 15 nm filters in series, without relevant loss of thrombin activity, is discussed on page 5, paragraph 1, and confirmed by the data reported in example 1 of the application (see the Table on page 7).

3.9 Since filters with a nominal pore size of 15 nm can retain even the smallest virus particles, it is credible that they will also retain lipid-containing virions (which are of larger size) still present in the purified thrombin material. In other words, nanofiltration is effective in removing both enveloped and non-enveloped viruses.

3.10 It is also plausible that a second filtration step carried out in series, albeit with the same pore size, may achieve a further reduction in viral load by retaining particles which for some reason were not retained by the first filter.

3.11 According to the appellant's letter dated 23 May 2014 (see page 5, Table 1), the appellant succeeded in achieving, by double nanofiltration (15 nm + 15 nm) applied to a thrombin formulation presumably in conformity with the definition of present claim 1, a reduction in the quantity of Porcine Parvovirus (PPV) by a factor of $10^{6.14}$. The appellant also mentioned on page 6 of that letter that according to experimental data obtained in a validation study, the second 15 nm filter will retain up to 3.31 ($\log_{10}$) units of PPV viruses that have passed through the first filter (also see the statement setting out the grounds of appeal in point III.3.2).

3.12 For these reasons and in the absence of conflicting data, the board considers that it has been rendered credible that an acceptable level of virus elimination can be achieved by double nanofiltration carried out in series through filters of a nominal pore size of 15 nm, as defined in claim 1.

3.13 Since supplementary virus inactivation or elimination steps are not needed, it is recognised that claim 1 achieves a process simplification.

3.14 The board therefore considers that, starting from the technical teaching of document D2, the objective technical problem is the provision of a simplified process for obtaining a thrombin composition with acceptable viral safety.

3.15 The solution to that problem is the process as defined in claim 1.

Obviousness of the solution

3.16 Document D2 itself does not suggest a second nanofiltration step and does not contain any pointer towards such a measure; nor does document D1, which has a similar general content.

3.17 Document D6 relates to the preparation of purified human ceruloplasmin and mentions that treatments for viral safety included the application of the SD method and two nanofiltration steps using 35- and 15-nm pore size filters. Thus, document D6 does not propose nanofiltration as the only process step needed for reducing the viral load. Regarding the nanofiltration steps themselves, D6 discloses pre-filtration with a pore size of 35 nm followed by a further filtration step employing a filter with a pore size of 15 nm,

rather than two filtration steps carried out in series with the same pore size of 15 nm.

3.18 The board, therefore, is of the opinion that the cited prior-art documents, without the use of hindsight, cannot lead the way to the process defined in claim 1.

3.19 As a consequence, the board concludes that the process according to independent claim 1 involves an inventive step within the meaning of Article 56 EPC. The same conclusion applies to the subject-matter of the dependent claims.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with the following claims and a description to be adapted:

Claims:

Claims 1 to 6 submitted in the oral proceedings of 28 February 2019

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated