Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 26 October 2020

Case Number: T 1180/18 - 3.3.07

Application Number: 05380116.3

Publication Number: 1656954

IPC: A61K51/08

Language of the proceedings: EN

Title of invention:
Therapeutic human albumin solutions with low prekallicrein activator (PKA) activity and process for obtaining them

Patent Proprietor:
Grifols, S.A.

Opponent:
CSL Behring GmbH

Headword:
Therapeutic human albumin solutions / GRIFOLS, S.A.

Relevant legal provisions:
EPC R. 103(1)(a)
RPBA Art. 12(4)
RPBA 2020 Art. 25(2), 13(1)
EPC Art. 114(2), 123(2), 123(3), 83, 54, 56

Keyword:

Reimbursement of appeal fee - substantial procedural violation (no)
Late-filed evidence - admittance of documents filed in appeal proceedings
(Late-filed) Requests - admittance in appeal proceedings
Amendments - main request, auxiliary requests 1-21 - extension beyond the content of the application as filed (yes) - auxiliary requests 22-31 - extension of protection (yes)
Sufficiency of disclosure - auxiliary request 32 (yes)
Novelty - auxiliary request 32 (yes)
Inventive step - auxiliary request 32 (yes)

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1180/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 26 October 2020

Appellant: (Patent Proprietor)	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)
Appellant: (Opponent)	CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg (DE)
Representative:	Pohlman, Sandra M. df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 27 March 2018 concerning maintenance of the European Patent No. 1656954 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 1 656 954 (hereinafter "the patent") was granted on the basis of 10 claims. Independent claims 1 and 9 of the patent as granted read as follows:

"1. Process for reducing the prekallicrein activator (PKA) activity in purified albumin solutions of human origin and for stabilising it over time, characterised by the partial extraction of the antithrombin during the fractionation of human plasma so that the final albumin has an active antithrombin content equal to or greater than 0.03 mg/g of albumin."

"9. Purified human albumin solution of human origin prepared by the process of claims 1 to 8, having an active antithrombin content of 0.03 to 0.10 mg/g of albumin, prekallikrein (PKA) activity below 35 IU/ml, and stability over time."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step and it was not sufficiently disclosed. The late filed ground of opposition according to Article 100(c) EPC was further admitted during opposition proceedings.

III. A first appeal on the same case was filed by the opponent against the decision of the opposition division posted on 3 January 2013 to reject the opposition. The competent board set aside the decision under appeal and remitted the case to the opposition division for further prosecution (T 598/13).

IV. At the end of the opposition proceedings following the remittal of the board, the opposition division took the interlocutory decision that, on the basis of the auxiliary request 20, the patent met the requirements of the EPC. The decision was based on the patent as granted as main request and on auxiliary requests 1-20. Auxiliary request 20 contained 8 claims, wherein claims 1-8 corresponded to claims 1-8 as granted.

V. The 2nd decision of the opposition division, posted on 27 March 2018, cited among others the following documents:

D8: Australasian Biotechnology, 1995, Vol. 6 issue 2
D9: British Journal of Anaestesia, 2000, 85(6), 887-895
D10: Hemostasis and Thrombosis, Basic Principles and Clinical Practice, 4th Edition, 2001, pages 69-72, 103-104 and 321-322
D11: Die gelben Hefte, 1998, 38, 81-88
D13: Principles and techniques of practical biochemistry, 4th Edition, 1994, 182-192
D16: Biotechnology and Blood Proteins, 1993, Vol. 227, 143-149
D20: Biochemical and Biophysical Research Communications, 1977, 74(1), 150-158
D21: 2nd Declaration of Michael Moses
D26: Clinical methods: The History, Physical and Laboratory Examinations, 3rd Edition, 1990, chapter 101
D27: The Biology of Antithrombins, CRC, 1990, page 50
D28: Blood coagulation, Biochemistry (Mosc.), 2002, Jan, 67(1), 3-12
D29: Drugs and Laboratory Parameters, 1st Edition, September 2010, page 34
D30: Grifols Thormbate product info Antithrombin III (Human), Thrombate III, August 2013

D31: Human Blood Plasma Proteins, Structure and Function, Wiley, 2008
Annex C: Instructions for use WHO International Standard 2nd International Standard Antithrombin
Annex G: Conrad J *et al.*, 1983
Annex H: Kalafatis M *et al.*, 1997
Annex L: Murano G *et al.*, 1980
D34: Römpp Chemie-Lexikon
D35a: Graph submitted by the appellant-opponent during 1st instance oral proceedings

VI. The opposition division decided in particular as follows:

(a) Documents "Annex E-L" were admitted into the opposition proceedings whereas D34 was not.

(b) The skilled person would have been able to determine the active antithrombin content in the sample. Furthermore, on the basis of the data provided in the patent it was credible that products having an antithrombin content of 0.03 mg/g of albumin were fairly stable. Thus, the patent was sufficiently disclosed.

(c) The subject-matter of the main request and auxiliary requests 1-17 did not comply with Article 123(2) EPC in view of the introduction of the value of 0.1 mg/g of albumin as upper limit for the amount of antithrombin in claim 9.

(d) The late filed auxiliary requests 18-19 were not admitted in the opposition proceedings.

(e) The subject-matter of auxiliary request 20 was was novel over Dll. Furthermore, starting from D9 as

closest prior art, the skilled person would not have considered introducing specifically a PKA inhibitor so as to provide albumin solutions with reduced and stable PKA activity.

VII. Both the patent proprietor (appellant-patent proprietor) and the opponent (appellant-opponent) lodged an appeal against the above interlocutory decision of the opposition division.

VIII. With its statement setting out the grounds of appeal the appellant-patent proprietor defended its case on the basis of the patent as granted as main request, and on the basis of auxiliary requests 1-34 filed therewith. Further auxiliary requests were filed on 20 December 2018 (auxiliary requests 32a, 33a and 34a) and on 14 October 2020 (auxiliary requests 10a and 10b).

The content of the claims upon which the present decision is based can be illustrated as follows:

Claim 9 of auxiliary request 1 read as follows:

"9. Purified human albumin solution of human origin for therapeutic use prepared by the process of claims 1 to 8, having an active antithrombin content of 0.03 to less than 0.10 mg/g of albumin, prekallikrein (PKA) activity below 35 IU/ml, and stability over time."

Auxiliary request 2 differed from auxiliary request 1 in that dependent claim 10 had been deleted.

Claim 9 of auxiliary request 3 differed from claim 9 of auxiliary request 1 in that the antithrombin

concentration range was amended to "of between 0.03 and 0.10 mg/g of albumin".

Auxiliary request 4 differed from auxiliary request 3 in that dependent claim 10 had been deleted.

Claim 9 of auxiliary request 5 differed from claim 9 of auxiliary request 1 in that the antithrombin concentration range was amended to "of 0.039 to less than 0.10 mg/g of albumin".

Claim 9 of auxiliary request 6 differed from claim 9 of auxiliary request 1 in that the antithrombin concentration range was amended to "between 0.039 and 0.10 mg/g of albumin".

Claim 9 of auxiliary request 7 differed from claim 9 of auxiliary request 1 in that the antithrombin concentration range was amended to "of 0.065 to less than 0.10 mg/g of albumin".

Claim 9 of auxiliary request 8 differed from claim 9 of auxiliary request 1 in that the antithrombin concentration range was amended to "between 0.065 and 0.10 mg/g of albumin".

Claim 9 of auxiliary request 9 read as follows:

"9. Purified human albumin solution of human origin prepared by the process of claim 6, having an active antithrombin content of between 0.03 and 0.10 mg/g of albumin, prekallikrein (PKA) activity below 35 IU/ml, and stability over time."

Claim 9 of auxiliary request 10 differed from claim 9 of auxiliary request 9 in that the following feature

was added, "wherein the antithrombin is extracted by heparin-agarose affinity chromatography".

Claim 9 of auxiliary request 10a differed from claim 9 of auxiliary request 10 in that the feature "for therapeutic use" was added.

Claim 9 of auxiliary request 10b differed from claim 9 of auxiliary request 10a in that the feature "and wherein the albumin is prepared from fraction V" was added.

Claim 9 of auxiliary request 11 read as follows:

"9. Purified human albumin solution of human origin prepared by the process of claims 1 to 8, having an active antithrombin content of 0.03 to 0.1 mg/g of albumin, prekallikrein activator (PKA) activity below 35 IU/ml, and stability over time."

Claim 9 of auxiliary request 12 differed from claim 9 of auxiliary request 1 in that the value of "0.10" was replaced by "0.1" and "prekallikrein (PKA) activity" was amended to "prekallikrein activator (PKA) activity".

Auxiliary request 13 differed from auxiliary request 12 in that dependent claim 10 had been deleted.

Claim 9 of auxiliary request 14 differed from claim 9 of auxiliary request 12 in that the antithrombin concentration range was amended to "between 0.03 and 0.1 mg/g of albumin".

Auxiliary request 15 differed from auxiliary request 14 in that dependent claim 10 had been deleted.

Claim 9 of auxiliary request 16 differed from claim 9 of auxiliary request 12 in that the antithrombin concentration range was amended to "of 0.039 to less than 0.1 mg/g of albumin".

Claim 9 of auxiliary request 17 differed from claim 9 of auxiliary request 12 in that the antithrombin concentration range was amended to "between 0.039 and 0.1 mg/g of albumin".

Claim 9 of auxiliary request 18 differed from claim 9 of auxiliary request 12 in that the antithrombin concentration range was amended to "of 0.065 to less than 0.1 mg/g of albumin".

Claim 9 of auxiliary request 19 differed from claim 9 of auxiliary request 12 in that the antithrombin concentration range was amended to "between 0.065 and 0.1 mg/g of albumin".

Claim 9 of auxiliary request 20 read as follows:

"9. Purified human albumin solution of human origin prepared by the process of claim 6, having an active antithrombin content of between 0.03 and 0.1 mg/g of albumin, prekallikrein activator (PKA) activity below 35 IU/ml, and stability over time."

Claim 9 of auxiliary request 21 differed from claim 9 of auxiliary request 20 in that the following feature was added, "wherein the antithrombin is extracted by heparin-agarose affinity chromatography".

Claim 9 of auxiliary request 22 read as follows:

"9. Purified human albumin solution of human origin prepared by the process of claim 6, wherein in said process from 50% to 80% of active antithrombin is extracted, wherein said solution has prekallikrein activator (PKA) activity below 35 IU/ml, and wherein said solution has stability over time."

Claim 9 of auxiliary request 23 differed from claim 9 of auxiliary request 22 in that the extraction was limited to 80%.

Claim 9 of auxiliary request 24 read as follows:

"9. Purified human albumin solution of human origin prepared by the process of claim 6, having prekallikrein (PKA) activity below 35 IU/ml, and stability over time, wherein in said process from 50% to 80% of active antithrombin is extracted."

Claim 9 of auxiliary request 25 differed from claim 9 of auxiliary request 24 in that the term "activator" was added.

Claim 9 of auxiliary request 26 differed from claim 9 of auxiliary request 24 in that the following feature was added, "by heparin-agarose affinity chromatography".

Claim 9 of auxiliary request 27 differed from claim 9 of auxiliary request 26 in that the term "activator" was added.

Claim 9 of auxiliary request 28 differed from claim 9 of auxiliary request 24 in that the percentage was limited to 80%.

Claim 9 of auxiliary request 29 differed from claim 9 of auxiliary request 28 in that the term "activator" was added.

Claim 9 of auxiliary request 30 differed from claim 9 of auxiliary request 28 in that the following feature was added, "by heparin-agarose affinity chromatography".

Claim 9 of auxiliary request 31 differed from claim 9 of auxiliary request 30 in that the term "activator" was added.

Auxiliary request 32 corresponded to the auxiliary request maintained by the opposition division. As indicated in point IV above, this request contained 8 claims corresponding to claims 1-8 as granted.

With the statement setting out the grounds of appeal the appellant-patent proprietor also requested the reimbursement of the appeal fee on the grounds of a substantial procedural violation committed by the opposition division.

IX. The following items of evidence were filed by the parties during the appeal proceedings:

(a) Documents filed by the appellant-opponent with its statement setting out the grounds of appeal:

D36: Declaration of Prof. Dr. Thierry Burnouf
D37: British Journal of Haematology, 1982, 52, 275-281
D38: 2nd Declaration of Michael Moses dated 6 August 2018
D39: Haematologica, 1998, 83, 305-311

(b) Documents filed by the appellant-patent proprietor with its reply to the opponent's statement setting out the grounds of appeal:

D57: Declaration of Dr. Isabel Bravo
D58: JBC, 1985, 260 (3), 1723-1729

(c) Documents filed by the appellant-opponent on 28 May 2019:

D59: 2nd Declaration of Prof. Dr. Thierry Burnouf
D59 annex 1: WHO recommendations for the production control and regulation of human plasma for fractionation
D59 annex 2:ISBT Science Series, 2014, 9, 160-167

(d) Document filed by the appellant-patent proprietor on 14 October 2020:

D60:Human plasma for fractionation, European Pharmacopoeia 5.0.

X. Oral proceedings were held before the Board on 26 October 2020.

XI. The appellant-patent proprietor requested that the decision under appeal be set aside and the patent be maintained as granted, or that the patent be maintained on the basis of one of auxiliary requests 1-34 filed on 6 August 2018 with the statement setting out the grounds of appeal, or auxiliary requests 32a, 33a, or 34a filed on 20 December 2018 with the reply to the grounds of the appellant-opponent, or on the basis of auxiliary requests 10a or 10b filed on 14 October 2020.

The appellant-patent proprietor also requested reimbursement of the appeal fee because of a substantial procedural violation in opposition proceedings. The appellant-patent proprietor furthermore requested that documents D57, D58 and D60 be admitted into the proceedings, that documents D34, D36-D39 and D59 (including annexes 1-2) be excluded from the appeal proceedings and that the novelty attacks based on D8, Dll, D16 and D9 not be admitted into the proceedings.

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

The appellant-opponent also requested that auxiliary requests 9-10,10a, 10b, 20-31, 32a, 33a and 34a not be admitted into the appeal proceedings. The appellant-opponent furthermore requested that documents D57 and D58 not be admitted should D36 not be admitted, that D60 not be admitted and that documents D34, D36-D39 and D59 be admitted into the appeal proceedings.

XIII. The arguments of the appellant-patent proprietor, as far as relevant for the present decision, can be summarised as follows:

(a) Alleged substantial procedural violation

The scope of the remittal to the opposition division in case T 598/13 was clearly limited to sufficiency of disclosure. Moreover, the facts underlying the first decision of the opposition concerning the criteria of Article 123(2) EPC did not change. The opposition division therefore did not observe the binding effect of the remitting decision when examining the main request for

compliance with the requirements of Article 123(2) EPC during oral proceedings. The opposition division consequently committed a substantial procedural violation and the appellant-patent proprietor was entitled to reimbursement of the appeal fee.

(b) Admittance of items of evidence

D34 was not *prima facie* relevant. The opposition division did correctly exercise its discretion not to admit this document.

D36-D39 could have been filed during the first instance proceedings. In particular D36, and consequently D37 cited therein, merely reiterates arguments that were already presented in first instance proceedings. Furthermore, the reliability of D21 had already been questioned by the appellant-patent proprietor in writing in first instance proceedings, so that the appellant-opponent had ample time to submit D36-D38 attempting to remedy this issue. Finally D39 was not submitted in response to a new point raised in the appealed decision and did not constitute evidence of common general knowledge as it was a research paper. Accordingly, D36-D39 were not to be admitted into the appeal proceedings.

D57-D58 were filed in direct response to D36 and the inventive step objection raised in the appellant-opponent's statement setting out the grounds of appeal, respectively. These documents were thus to be admitted in the appeal proceedings.

D59 and annexes 1-2 were not to be admitted because they merely supported arguments already made in D36 and could therefore have been filed earlier.

(c) Main request

The higher end value introduced in claim 9 was based on example 1, table 1 of the original application. This value corresponded to the higher value of active antithrombin in the absence of a specific extraction step. This value could be generalised to the products of present claim 9, so that claim 9 of the main request did thus fulfill the requirements of Article 123(2) EPC.

(d) Admittance of auxiliary requests 10 and 24-31

Auxiliary requests 10 and 24-31 were filed in reaction to the surprising decision of the opposition division considering the main request as infringing Article 123(2) EPC and were therefore to be admitted into the appeal proceedings.

(e) Auxiliary requests 1-21, 10a and 10b

Claim 9 of auxiliary requests 1-21, 10a and 10b met the requirements of Article 123(2) EPC for the same reasons as developed for the main request. In particular the restriction of claim 9 of auxiliary request 10 to partial extraction from the specific fractions II+III supernatant by heparin-agarose affinity chromatography limited the process by which the claimed product was obtainable to the necessary features of the original example, so that the argument of an alleged intermediate generalisation no longer applied. The additional

features introduced in auxiliary requests 10a and 10b brought the respective claims 9 even further in line with the original example.

(f) Auxiliary requests 22-31

In claims 9 of auxiliary requests 22-31, the active antithrombin content was replaced by the percentage of extraction of (active) antithrombin. The presently claimed range of 50-80% extraction as well as the presently claimed specific value of 80% extraction defined a restricted number of products falling under the scope of granted claim 9 as well as granted claim 1 due to the principle of extension of protection from a process to the product directly obtained therefrom according to Article 64(2) EPC. The scope of claims 9 of auxiliary requests 22-31 did thus not extend beyond scope of the granted claims.

(g) Auxiliary request 32

(i) The skilled person would be able to determine the final concentration in active antithrombin in mg *per* g of albumin by using routine tests (chromogenic, immunogenic, active site titration assays). The patent provided guidance on how to prepare an albumin solution containing the claimed amount of antithrombin, namely by partial extraction of antithrombin whose conditions could be adapted if needed (see example and paragraph [0011]). Furthermore table 2 substantiated that PKA activity could be reduced and stabilised over time when performing partial antithrombin

extraction so as to maintain at least 0.03mg active antithrombin *per* g of albumin. Finally the appellant-opponent did not provide any experimental data substantiating that the invention could not be carried out. Auxiliary request 32 was therefore sufficiently disclosed.

(ii) D11 did not disclose any albumin solution having an active antithrombin content within the presently claimed range. An implicit disclosure of such a solution could further not be provided by D11, since D11 only disclosed a total extraction of antithrombin *via* heparin adsorption chromatography. Claim 1 of auxiliary request 32 was consequently novel.
The novelty objections newly raised by the appellant-opponent based on D8, D9 and D16 should not be admitted into the appeal proceedings.

(iii) D9 represented the closest prior art. D9 generally taught that PKA activity was an issue in albumin solutions and may cause hypotensive effects, so that the developed processes aimed at removing PKA from the solutions. The distinguishing feature of claim 1 over D9 was the partial extraction of active antithrombin so as to maintain a minimum amount of active antithrombin in the final solutions. This had the effect of inhibiting PKA activity, in particular over time, and to reduce hypotensive risks.
The objective technical problem to be solved was thus the provision of a process

for the preparation of an improved albumin solution with significant stability of PKA levels. D9 merely pointed towards the removal of PKA from the solutions and did not suggest the use of a PKA inhibitor. The other prior art documents did also not suggest a partial active antithrombin extraction to solve the problem posed. In particular D13 was not concerned with albumin solutions, D10 described antithrombin III as an inefficient PKA inhibitor and D20 was an isolated scientific publication which the skilled person would have had no incentive to combine with D9. Hence the subject-matter of auxiliary request 32 involved an inventive step.

XIV. The arguments of the appellant-opponent, as far as relevant for the present decision, can be summarised as follows:

(a) Alleged substantial procedural violation

In T 598/13, the Board explicitly stated that it refrained from taking intermediate decisions on any other grounds of opposition. Hence, the *ratio decidendi* of the Board's decision did not bind the opposition division on any Article. As a result the opposition did not commit any substantial procedural violation.

(b) Admittance of items of evidence

D34 was *prima facie* relevant and constituted evidence of common general knowledge that could be filed at any time in the proceedings.

D36-37 were filed in direct response to the first instance decision and were therefore admissible.

D57-D58 related to arguments which could have been filed earlier and were not to be admitted. However these documents could be admitted in the appeal proceedings if the documents filed by the appellant-opponent during appeal proceedings, including D59 and the annexes thereto, were admitted.

D59 and annexes 1-2 were filed to provide a further explanation to the antithrombin content variability in plasma pools, based on donor to donor variability. This was a new point submitted in direct response to the declaration of D57 and in addition to D36.

(c) Main request

The introduction of the higher end value of the active antithrombin content in claim 9 of the main request constituted an unallowable generalisation of the value disclosed in the specific original example 1. Said value was obtained under very specific conditions and was dependent thereupon. In particular the initial active antithrombin content would vary from sample to sample and from plasma pool to plasma pool. Moreover a process dependent loss of active antithrombin during plasma fractionation, for example due to denaturation, could also occur. Neither the original example nor

the claims were limited to plasma pool as starting material and the claims recited any plasma fractionation process. Accordingly, claim 9 of the main request did not meet the requirements of Article 123(2) EPC.

(d) Admittance of auxiliary requests 10 and 24-31

Auxiliary requests 10 and 24-31 were not to be admitted because they should have been filed earlier. In particular re-examination of the main request for compliance with the requirements of Article 123(2) EPC should have been expected at least in the light of the preliminary opinion of the Board in case T 598/13.

(e) Auxiliary requests 1-21, 10a and 10b

Claim 9 of auxiliary requests 1-21 did not fulfill the requirements of Article 123(2) EPC essentially for the same reasons as developed for the main request.

(f) Auxiliary requests 22-31

The removal of the final active antithrombin concentration and its replacement with an antithrombin extraction percentage in claims 9 resulted in extending the scope of protection conferred by the granted claims because the variability in initial active antithrombin content and the variability of its loss during plasma fractionation, influenced the absolute value of final active antithrombin content. As a result the present claims 9 encompassed products not covered by granted claim 9 contrary to Article 123(3) EPC .

Besides, the scope of granted claim 1 covered, according to Article 64(2) EPC, merely the product directly obtained by the claimed process and did therefore not encompass the entire scope of present claims 9.

(g) Auxiliary request 32

(i) The skilled person could not perform the claimed process without undue burden. In particular:

- The skilled person could not determine the content in active antithrombin of the final albumin solutions in mg/g albumin. This unit would require the use of a conversion factor. The use of different assays to determine said conversion factor for each sample would not be industrially feasible.
- The patent did not provide sufficient guidance on how to achieve the claimed minimal active antithrombin concentration. This value would be process dependent, as revealed by D21.
- The claimed stability was not achieved (the PKA activity did not remain at its initial level, see table 2), in particular not for solutions having a low content in active antithrombin (*i.e.* close to 0.03mg/g albumin).

The auxiliary request 32 was consequently not sufficiently disclosed.

(ii) Every standard fractionation process involving the fractions FII/FIII of the Cohn process would lead to partial

antithrombin depletion (see D36), which would amount to a partial extraction. D11, as well as D8, D9 and D16, in so far as they disclosed the Cohn process, anticipated the subject-matter of claim 1 of auxiliary request 32.

(iii) D9 represented the closest prior art. In particular the Cohn process disclosed in Figure 1 constituted the closest prior art embodiment.

The distinguishing feature of claim 1 of auxiliary request 32 over D9 was the partial extraction of active antithrombin (no specific extraction thereof in the Cohn process of D9). Processes according to the Cohn process achieved at least as good results as the process according to the invention (see table 2 of the patent in suit). No effect directly resulting from the difference had thus been substantiated. The objective technical problem to be solved was therefore the provision of an alternative process for the preparation of an albumin solution by plasma fractionation.

According to D13 it would be common general knowledge, when purifying proteins, to either remove proteases or to keep proteases inhibitors. Active antithrombin would be commonly known as an inhibitor of PKA (see D10). Maintaining some antithrombin in the albumin solution during plasma fractionation would thus be an

obvious alternative for the skilled person willing to solve the problem posed. Also the combination of D20 (describing the inhibitory effect of active antithrombin on PKA) with D9 would render the claimed subject-matter obvious. Claim 1 of auxiliary request 32 did thus not fulfill the requirements of Article 56 EPC.

Reasons for the Decision

1. Alleged substantial procedural violation

1.1 In the statement setting out the grounds of appeal the appellant-patent proprietor requested reimbursement of its appeal fee on the basis of an alleged substantial procedural violation committed by the opposition division.

1.2 The Board notes that the order of the competent Board in T 598/13 was the remittal of the case to the opposition division "for further prosecution". The reasons for the decision are decisive for the decision's binding effect on the opposition division. In this context, the reasoning as regards the grounds of opposition in T 598/13 is limited to that under Article 100(b) EPC. In relation to the request of the appellant-opponent for a decision on the other grounds of opposition, paragraph 3.4 of decision T 598/13 further specifies that "the Board considers it appropriate to refrain from taking partial decisions that may potentially have an impact on the further prosecution of the case". It follows that decision T 598/13 contains no reasoning concerning the other grounds by which the opposition division could be bound.

It is noted that the mention in paragraph 3.1 of the decision that the case was to be remitted "for a substantive examination of the ground pursuant to Article 100 (b) EPC" cannot be interpreted as limiting the scope of examination upon remittal since it was made merely in the context of presenting the reasons for a remittal. The Board hence considers that the remittal did not limit the opposition division to examine only the ground of opposition under Article 100(b) EPC.

1.3 The Board further notes that the interpretation by the opposition division of the results of the patent's example changed following the admittance of new evidence filed during appeal case T 598/13. The disputed amendments being based on a feature of said example, the opposition division was led to re-examine the issue of compliance with Article 123(2) EPC. The Board considers that the change of underlying facts constitutes a sufficient reason for the opposition division to re-examine the issue of compliance with the requirements of Article 123(2) EPC.

1.4 The Board therefore concludes that the opposition division did not commit a substantial procedural violation. The request for reimbursement of the appeal fee is therefore refused (Rule 103(1)(a) EPC).

2. Admittance of items of evidence

2.1 Document D34

Document D34 was filed by the opponent on 13 October 2017 during the first instance proceedings as evidence of common general knowledge concerning the definition

of the term "stability". The opposition division did not admit said late-filed document into the opposition proceedings because it was not *prima facie* relevant.

In the Board's view the opposition division exercised its discretion under Article 114 (2) EPC by applying the correct criteria. There is no indication that this has been done in an unreasonable way. In particular, while the interpretation of the feature relating to "stabilising" the PKA activity over time in the context of claim 1 of the main request appeared to differ amongst the parties and the opposition division, the common meaning of the term "stability" did not appear to be disputed. The late filing of evidence of common general knowledge of the meaning of said term does thus not appear to be required. Hence, the Board sees no reason to overrule the decision not to admit document D34.

2.2 Documents D36-D39 and D57-D58

Documents D36-D39 were filed by the appellant-opponent with its statement setting out the grounds of appeal and documents D57-D58 were filed by the appellant-patent proprietor with its reply thereto. Both submissions were filed before 1 January 2020. Their admittance must be decided on the basis Article 12(4) RPBA 2007, which gives the Board discretion not to admit them if they should have been presented in the first instance proceedings (Article 25(2) RPBA 2020).

2.2.1 D36-D39 relate to the issue of antithrombin concentration in plasma and to the possibility of expressing it in mg/g of albumin as well as to the issue of the reliability of the experiments reported in D21. The Board notes that the determination of the

content of active antithrombin in the albumin solutions was a key point in the first instance proceedings as well as in the previous appeal T 598/13. However, the assessment of this issue has evolved during the first instance proceedings, as revealed by the statement made on page 4 of the second decision of the opposition division posted on 27 March 2018, namely that "the discussion on sufficiency unveiled other aspects of the claimed subject-matter". The Board further notes that the opposition division did not address this issue in its preliminary opinion accompanying the summons to attend oral proceedings dated 23 February 2017. The issue became only pertinent during the oral proceedings before the opposition division. Documents D36-D39 were thus filed in reaction to the decision of the opposition division.

Hence, the Board does not exercise its discretion pursuant to Article 12(4) RPBA 2007 to exclude these documents from the appeal proceedings. D36-D39 thus form part of the appeal proceedings.

2.2.2 Documents D57-58 have been filed in response to the declaration contained in D36 and to the inventive step argumentation of the appellant-opponent developed in its statement setting out the grounds of appeal.

Hence, the Board does not exercise its discretion pursuant to Article 12(4) RPBA 2007 to exclude these documents from the appeal proceedings. D57 and D58 thus form part of the appeal proceedings.

2.3 Document D59 and annexes 1-2

Document D59 and the annexes thereto were filed by the appellant-opponent with its letter dated 28 May 2019.

The filing of this additional piece of evidence constitutes an amendment to that party's case and D59 may be admitted only at the discretion of the Board (. Article 13(1) RPBA 2020).

The Board notes that, despite the statement made in D59 that this document would be in direct response to the declaration of D57, D59 mainly concerns the issue of antithrombin content variability from plasma pool to plasma pool. The previous declaration of Dr. Burnouf, D36, was however already extensively addressing this issue. The fact that D59 and the annexes thereto may provide a further explanation for the antithrombin content variability from plasma pool to plasma pool does not render the overall issue new. Annexes 1 and 2 to D59 could already have been filed in support of D36, and it is also not clear how D59 could assist further in overcoming the objections raised. Furthermore, in the two last paragraphs of D59, the appellant-opponent appears to merely repeat an argument that was already developed in its letter of 28 May 2019.

Document D59 and annexes 1-2 are thus not admitted into the appeal proceedings.

Main request

3. Amendments - Article 123(2) EPC

3.1 Claim 9 of the main request corresponds to original claim 9 which was reworded as a product-by-process claim and wherein *inter alia* a higher end value, namely 0.10 mg/g of albumin, was introduced for the active antithrombin content range.

3.2 This value is based on the disclosure of said concentration in original table 1. This table provides the results of example 1, which relates to a process of plasma fractionation wherein either no specific antithrombin extraction step was performed or an antithrombin extraction from various proportions (50, 80, 100%) of the fractions II+III supernatant was done. The value of 0.1 mg/g of albumin corresponds to the final concentration of active antithrombin when no specific extraction is performed. This value was however obtained for a very specific fractionation process (see paragraphs [0014], [0016] and [0017] of the patent specification) while claim 1, to which claim 9 refers by means of the product-by-process formulation, does not contain any limitations with regard to the fractionation process (neither the process steps nor the starting plasma). The introduction of this specific value in granted claim 9 presupposes, in order to fulfill the requirements of Article 123(2) EPC, that this value could be generalised to any type of plasma fractionation process (*i.e.* any process steps and any starting material).

3.3 The Board is however not convinced that this condition is satisfied for the following reasons:

(a) The prior art reveals that the amount of active antithrombin varies from plasma sample to plasma sample (see *inter alia* D27, page 50; D28, table 1; D29, page 3; D30, page 1; D31, page 301; Annex G, table 1; Annex H, page 257, 2nd column; Annex L, "Introduction"; D36, page 2 points 8-9.) so that the amount of active antithrombin in the final albumin solutions in the absence of any specific antithrombin extraction would necessarily also vary. Hence, the final active antithrombin content

obtained starting from one specific sample cannot be generalised to any other one.

In this context, the appellant-patent proprietor referred to the declaration D57 to argue that the use of plasma pools addresses this issue and provides uniformity by balancing said variations . Furthermore, it argued that due to the therapeutic use aimed at in the patent, the skilled person would recognise that plasma pools must be used. As a result the skilled person would understand that both the example of the granted patent and the process of claim 1 would be limited to plasma pools as starting material.

Independently of whether plasma pools indeed afford active antithrombin content uniformity or not, the Board notes that there is no indication in the original application that example 1 was performed using a plasma pool as starting material. The fact that the original application generally relates to therapeutic solutions does not necessarily imply that the example, illustrative of the claimed process and not followed by any therapeutic use, was performed starting from a plasma pool. It cannot therefore be concluded that the value obtained in said specific example would be representative of plasma pools.

(b) As explained in D36 (see in particular point 9) active antithrombin may be lost during plasma fractionation even in the absence of a specific antithrombin extraction step. According to the appellant-patent proprietor the skilled person would however understand that the process described in the granted patent and illustrated in example 1

corresponds to the Cohn process, in view of the reference to the fractions II, III and V. The Cohn process would thus be recognised as an overriding requirement of the patent and interpreted as an essential feature of the claims. The active antithrombin loss would be constant for a given process, so that it would be identical for any claimed product-by-process and the present example. In addition, the appellant-patent proprietor argued that the appellant-opponent did not provide evidence of variability of antithrombin loss.

The Board cannot share this conclusion. While plasma fractionation is illustrated in the description and the specific example with a process according to the Cohn process, there is no mention of the Cohn process in the granted patent. Neither the description nor the wording of the claims allow to conclude that the claims would be limited to any specific process. It follows that claim 9 is not limited to the product of the Cohn process, in particular not to the one of example 1 of the granted patent. Furthermore, even amongst processes according to the Cohn process, several parameters may vary (e.g. the ethanol content and pH of each fractionation step, see D11 Figures 1-2, D57 paragraph 6 and D36 paragraph 14). This may in turn influence active antithrombin loss. There is no evidence that the loss of active antithrombin would be identical for various plasma fractionation processes depending on the nature of the separation steps involved. Hence, it is not directly and unambiguously derivable from the original application that the final active antithrombin content in albumin solutions obtained following a specific plasma fractionation process can be

generalised to albumin solutions obtained by any other process.

3.4 In conclusion, there is no basis to generalise the specific value obtained in example 1 to products obtained from any claimed plasma fractionation process using any starting material. Accordingly, the introduction of this specific value in claim 9 of the main request infringes Article 123(2) EPC.

Admittance of auxiliary requests

4. Auxiliary requests 10 and 24-31

4.1 Auxiliary requests 10 and 24-31 were newly filed with the appellant-patent proprietor's statement setting out the grounds of appeal before 1 January 2020. Their admittance must be decided on the basis Article 12(4) RPBA 2007 (Article 25(2) RPBA 2020).

4.2 These requests are aimed at overcoming the opposition division's finding of lack of compliance with the requirements of Article 123(2) EPC of claim 9 of the main request and auxiliary requests 1-17. The Board observes that, in the course of the proceedings before the opposition division, a negative opinion under Article 123(2) EPC was provided from the opposition division for the first time during the oral proceedings. Hence, the Board considers that auxiliary requests 10 and 24-31 represent a legitimate and direct response to the first-instance decision.

4.3 Accordingly the Board see no reason to exercise its discretion under Article 12(4) RPBA 2007 to exclude these requests from the appeal proceedings. Auxiliary

requests 10, 24-31 are thus considered in these proceedings.

5. No decision on the admittance of auxiliary requests 9, 10a, 10b and 20-23 was required as the findings concerning the lack of compliance with the EPC of the main request and auxiliary requests 10 and 24-31 applied thereto (see points 6. and 7.)

Auxiliary requests 1-10, 10a, 10b and 11-21

6. Amendments - Article 123(2) EPC

6.1 The Board considers that the reasoning developed concerning claim 9 of the main request (see points 3.1 to 3.4) applies *mutatis mutandis* to auxiliary requests 1-10, 10a, 10b and 11-21. The various amendments performed in claims 9 of said auxiliary requests do not overcome the issue of intermediate generalisation of the specific value obtained in example 1, for the following reasons:

(a) Several amendments made, namely the **exclusion of the end value(s) of the antithrombin content range** by the introduction of the expressions "less than" (auxiliary requests 1, 2, 5, 7, 12, 13, 16 and 18) or "between" (auxiliary requests 3, 4, 6, 8-10, 10a, 10b, 14, 15, 17 and 19-21), the **modification of the lower end value of said range** (auxiliary requests 5-8 and 16-19), the **replacement of 0.10 mg/g by 0.1 mg/g** (auxiliary requests 11-21), the introduction of the term "**activator**" (auxiliary requests 11-21), do not address the issue of intermediate generalisation raised for claim 9 of the main request with regard to the higher end value of the antithrombin content

range. In particular, the explicit exclusion of the end value of 0.10 mg/g by means of the terms "less than" or "between" does not overcome the objection relating to the fact that said value was generalised to processes extending beyond the original example. The issue under Article 123(2) EPC as detailed for the main request was indeed not whether the specific value would be reached or not, but its generalisation as the maximal obtainable antithrombin content for any fractionation process.

(b) The explicit limitation to **"for therapeutic use"** (auxiliary requests 1-8, 10a, 10b, 12-19), which, according to the appellant-patent proprietor, is meant to limit the claims to plasma pools as starting plasma material, does not overcome the issue linked to the generalisation of the original example. As detailed for the main request, the original application provides no indication that the value obtained in example 1 is indeed representative of a fractionation process using a plasma pool as starting material (see point 3.3 (b)).

(c) The limitation to the extraction of antithrombin from **fraction II+III supernatant** (auxiliary requests 9-10, 10a, 10b and 20-21) does not, contrary to the appellant-patent proprietor's opinion, limit the claims to the Cohn process, let alone to the specific process of original example 1. Other fractionation processes involving said fractions are indeed known, see D9 figure 1. The Board observes that the further specification of said extraction being performed by **heparin-agarose affinity chromatography** (auxiliary requests 10, 10a, 10b and 21), introduced in an attempt to bring

the claims more in line with the original example 1, is not relevant with regard to the higher end value of antithrombin content. This value corresponds indeed to the antithrombin content in the absence of any purposive extraction, *i.e.* in the absence of said chromatography step.

(d) As argued by the appellant-patent proprietor, the further limitation to albumin extraction from **fraction V** in combination with the antithrombin extraction from fraction II+III supernatant in auxiliary request 10b appears to limit the claims to a Cohn fractionation process. However, as argued by the appellant-opponent, some parameters, such as the ethanol concentration and pH of the various fractionation steps, may still vary amongst Cohn fractionation processes and thus affect the loss of active antithrombin during fractionation. It cannot therefore be directly and unambiguously derived from the original application that the antithrombin concentration obtained in the absence of a specific extraction step in original example 1 would be the same for any type of process as defined in claim 9 of auxiliary request 10b.

6.2 Accordingly, auxiliary requests 1-10, 10a, 10b and 11-21 do not fulfill the requirements of Article 123(2) EPC.

Auxiliary requests 22-31

7. Amendments - Article 123(3) EPC

7.1 In auxiliary requests 22-31, the feature of claim 9 of the previous requests relating to the final active antithrombin content expressed in mg *per* g of albumin

was replaced by a feature defining a percentage of (active) antithrombin being extracted, based, according to the appellant-patent proprietor, on table 1 of example 1.

7.2 As explained in detail in the context of the main request and auxiliary requests 1-21, the Board considers that the final content of active antithrombin is dependent on the starting plasma and on the process dependent active antithrombin loss occurring during plasma fractionation in addition to the extraction rate. The Board therefore does not share the opinion of the appellant-patent proprietor that the content of active antithrombin would be directly dependent on the percentage of extraction. Contrary to the appellant-patent proprietor's view, the range provided in granted claim 9 for active antithrombin content does not generally correspond to 0-100% (active) antithrombin extraction. Said range merely corresponds to extraction of antithrombin from 0-100% of the volume of the FII+III supernatant in the particular case of the process of example 1. Example 1 being one specific plasma fractionation process, it cannot provide any universally applicable correlation between the percentage of fraction from which antithrombin has been extracted and the corresponding final active antithrombin content. The Board further considers that, as for auxiliary requests 1-21, none of requests 22-31 is limited to the specific process of example 1. It follows that it cannot be concluded that the product as now defined in claim 9 of auxiliary requests 22-31 would necessarily have a final active antithrombin content within the range of granted claim 9.

7.3 The appellant-patent proprietor further argued that, given the fact that the extraction percentage in

present claims 9 is limited to a narrow range (50-80%) or even a specific value (80%), the products of present claims 9 would necessarily fall within the scope of granted claim 9 which defines the broadest possible range (*i.e.* 0.03-0.10 mg/g final active antithrombin content which would correspond to 0-100% extraction). In view of the lack of any general correlation between the final active antithrombin content and the percentage of fraction from which antithrombin was extracted (see point 7.2), the Board considers that the choice of a narrow claim or even a discrete value does not change its conclusion.

7.4 The appellant-patent proprietor furthermore argued that the assessment of compliance with Article 123(3) EPC was to be based on the scope of protection provided by the granted claims as a whole. According to Article 64(2) EPC, granted claim 1, defining a partial extraction process, covered also the direct product obtained by said process. It followed that the granted claims as a whole covered an albumin solution obtained using any partial antithrombin extraction percentage, *i.e.* including 50-80%.

The Board agrees with the appellant-patent proprietor that granted claim 1 provides protection for the product directly obtained from said process. However claim 9 of each of auxiliary requests 22-31 contains both product-by-process and product features and defines thus a different scope. In addition, these claims, even if worded as product by process claims, have to be regarded as product claims *per se* when determining the extent of protection conferred by them. It follows that the protection conferred by them extends to any process for the preparation of the

claimed product, *i.e.* also processes not falling under granted claim 1.

7.5 The scope of protection of claim 9 of each of auxiliary requests 22-31 consequently extends beyond the one of the granted claims.

Auxiliary request 32

8. Amendments

Auxiliary request 32 corresponds to auxiliary request 20 on the basis of which the patent was maintained in amended from in first instance proceedings. Said request differs from the main request in that the process claims 9-10 were deleted.

The appellant-opponent did not raise any objection regarding the compliance with Articles 123(2) and 123(3) EPC of auxiliary request 32. The Board considers that auxiliary request 32 fulfills the requirements of Articles 123(2) and 123(3) EPC.

9. Sufficiency of disclosure

9.1 Claim 1 of auxiliary request 32 relates to a process for reducing and stabilising over time prekallikrein activator (PKA) activity in purified albumin solutions by performing a partial antithrombin extraction during plasma fractionation so that the final albumin solution has an active antithrombin content equal to or greater than 0.03 mg/g of albumin.

9.2 The following aspects were discussed:
(i) the determination of the active antithrombin content,

(ii) the achievement of the claimed active antithrombin content, and
(iii) the interpretation of stabilisation/stability over time and its achievement.

9.3 Determination of active antithrombin content

9.3.1 The content of active antithrombin is usually determined in terms of IU/mL. The conversion of this value in the presently used unit (mg/g of albumin) requires a conversion factor.

9.3.2 The Board agrees with the opposition division that the conversion factor could be determined for each starting plasma sample by measuring the antithrombin activity (chromogenic assay) as well as the total antithrombin content (ELISA assay) and combining said values. The thus obtained conversion factor should be representative of active antithrombin as denaturation should not have yet occurred in the starting plasma. It could then be applied to the value obtained for antithrombin activity in the final solutions so as to determine the content of active antithrombin in the claimed unit.

Furthermore, as underlined by the appellant-patent proprietor, active site titration is a further known method available to the skilled person to determine the content of active antithrombin (see for example Annex G, page 367 left column, 3rd paragraph and D57 point 8.). Alternatively, as described in D39 (see in particular page 309, paragraph "discussion"), inactive and active antithrombin could be separated by chromatography and thus the ratio of active/inactive antithrombin could be determined.

The Board is therefore not convinced by the argument of the appellant-opponent that the potential denaturation of antithrombin during plasma fractionation would necessarily prevent the skilled person from determining the active antithrombin content in the final albumin solutions.

The opponent finally argued that such measurements would not be feasible in practice at industrial scale. The fact that the method might be more time consuming does however not prevent the skilled person from performing the invention without undue burden.

9.3.3 Hence, the Board considers that there were methods available to the skilled person at the filing date of the granted patent to determine the content of active antithrombin in mg/g of albumin without undue burden.

9.4 Achievement of the claimed active antithrombin content

9.4.1 The Board observes that the granted patent provides an example of partial antithrombin extraction during plasma fractionation resulting in an albumin solution containing at least 0.03 mg of active antithrombin *per* g of albumin. The granted patent (see paragraph [0011]) further provides indications to adapt the chromatographic extraction conditions so as to reduce antithrombin extraction and maintain the content of active antithrombin at at least 0.03 mg *per* g of albumin. It moreover appears to be known to the skilled person that the fractionation process itself (*i.e.* the process steps, for example, in the case of the Cohn process, the pH and ethanol concentration, see D11 Figures 1-2, D57 §6 and D36 §14), even in the absence of any purposive (chromatographic) extraction step, may lead to a loss of active antithrombin. The skilled

person would thus have been aware of the possible necessity of adapting said process conditions to achieve the claimed value without undue experimentation.

9.4.2 According to the appellant-opponent, such an adjustment would not be feasible on a commercial scale. The Board observes however that the mere foreseen difficulty to adapt a process on a commercial scale does not preclude the skilled person from performing plasma fractionation with partial antithrombin extraction so as to achieve the presently claimed content of final active antithrombin.

9.4.3 The arguments of the appellant-opponent concerning the results obtained in D21, in which a plasma fractionation process without any antithrombin extraction did not achieve the claimed minimal antithrombin concentration, are not considered convincing by the Board for the following reasons:

(a) The credibility of the results provided in D21 is still questionable. Indeed D38, while acknowledging the occurrence of an error in the value obtained for a commercial solution of the proprietor did merely state that the remaining values of D21 would be reliable. However only the commercial solution was re-measured, not the remaining solutions of D21. It follows that some uncertainty remains as to the accuracy of the other values provided in D21.

(b) Even if the values of D21 were to be considered reliable, the mere fact that one specific plasma fractionation process does not lead to the claimed value does not necessarily indicate that the skilled person would not be able to perform the invention by adequately adjusting the process conditions.

9.4.4 Finally, the appellant-opponent's argument that the minimal concentration of 0.03 mg/g obtained in the very specific example of the patent could not be generalised to any fractionation process is not convincing when assessing sufficiency of disclosure in the present case. As detailed above under 9.4.1, the Board is of the opinion that the patent provides guidance as to how to achieve said value. For the reasons further detailed under 9.4.3 above, the opponent has not provided credible experimental data substantiating the contrary.

9.5 Interpretation of stabilisation/stability over time and its achievement

9.5.1 Concerning the interpretation of the feature "stabilising PKA activity over time", the Board notes that the patent does not provide for any definition of said functional feature. However, as is observed in the first appeal T 598/13, the whole teaching of the patent allows to distinguish between stable solutions (processes 1-6 in table 2) and unstable solutions (processes 7-8 in table 2). Indeed the increase in PKA activity is significantly more important in processes 7-8 (100% extraction) than processes 1-6 (0, 50 and 80% extraction). The Board does therefore not share the interpretation of said feature as made by the appellant-opponent, namely that the PKA activity should stay at its initial (decreased) level.

9.5.2 Hence, the Board is satisfied that the data provided in table 2 of the granted patent substantiate that the solutions prepared in the example with antithrombin extraction from up to 80% of the supernatant of fractions I+II indeed achieve the claimed stability.

9.5.3 The main point of dispute however lies in the issue of the stability of PKA activity over time in the case of albumin solutions obtained by antithrombin extraction from 80% to almost 100% of the supernatant of fractions II+III. The present patent does not provide any experimental data concerning PKA activity for such solutions.

9.5.4 The parties extensively discussed the possibility to extrapolate data obtained in Table 2 to solutions with antithrombin extraction in said range. The discussion focused mainly on the graphical representation of the data of table 2 submitted by the appellant-opponent during the oral proceedings before the opposition division. The Board considers that, in the absence of any experimental data concerning PKA activity over time for albumin solutions obtained by antithrombin extraction from 80% to almost 100% of the supernatant of fractions II+III, as well as in the absence of any (universal) correlation between said percentage of volume subjected to extraction and the final antithrombin concentration (*i.e.* being above 0.03 mg/g of albumin or not), no conclusions can be drawn as to the stability of said solutions. Any attempt to extrapolate the data of table 2 to solutions with more antithrombin extraction would be merely speculative.

9.5.5 It remains however that the patent as a whole and in particular the data of table 2 substantiate that, by maintaining some amount of antithrombin in the final albumin solutions (*i.e.* by performing partial extraction), the PKA activity can be lowered and stabilised over at least 12 months. The Board observes that the patent does not provide a clear limit for the maximum percentage of volume of supernatant of fractions II+III from which antithrombin can be

extracted while still maintaining stability of PKA activity over time. It would nevertheless be readily apparent for the skilled person that said limit would be between 80 and 100%. The skilled person would thus readily recognise from the teaching of the patent as a whole that, should the stability of PKA activity over time not be achieved for a given solution, then less antithrombin should be extracted.

A minimal value for the antithrombin content in the final solutions was furthermore set in the patent at 0.03 mg antithrombin *per* g of albumin. With regard to said value, the appellant-opponent has extensively argued that the patent would not provide any correlation between said minimal concentration and the claimed stability (due in part to auto-activation phenomena of PKA, see D10 page 69 and paragraph [0003] of the patent in suit). In this regard, the Board observes that in the context of the examples of the patent in suit (Tables 1 and 2), it appears credible that some stabilisation of PKA activity can be achieved at said concentration (antithrombin thus also limiting the feedback loop of PKA). In the absence of any experimental data substantiating that, for said value the claimed stabilisation of PKA activity over time is not achieved, the Board considers that the patent provides sufficient guidance to the skilled person to prepare an albumin solution with stabilised PKA activity over time as defined in the claims.

9.5.6 In this context the appellant-opponent argued that the provision of experimental data to substantiate a lack of sufficiency of disclosure is not a requirement and referred to the Case Law of the Boards of Appeal of the EPO, 9th Edition, II.C.9, page 394. The appellant-opponent considered that it had provided a lot of

substantiation that there would be reasonable doubts that the claimed stabilisation effect would not be achieved over the entire breadth of the claims. The Board cannot share this approach. In the cases referred to in said passage of the Case Law of the Boards of Appeal the opposed patent did not provide any detailed information as to how to put the invention into practice. As detailed above, the present case is different because general guidance, illustrated by specific examples, of how to carry out the claimed process and achieve the claimed effect is provided in the patent in suit.

9.6 In the Board's view, there are therefore no serious doubts, substantiated by verifiable facts, that the granted patent together with common general knowledge would allow the skilled person to perform the claimed invention without undue burden.

10. Novelty

10.1 Novelty with regard to D11

10.1.1 The novelty of auxiliary request 32 with respect to D11 was discussed and acknowledged in the appealed decision. The objection of the appellant-opponent based on D11 thus forms part of the appeal proceedings and cannot be excluded, as requested by the appellant-patent proprietor in the reply to the appellant-opponent's statement setting out the grounds of appeal.

10.1.2 Claim 1 of auxiliary request 32 defines "the partial extraction of the antithrombin during fractionation of human plasma" such that the final albumin solutions contain at least 0.03 mg active antithrombin *per* g of albumin. The Board considers that the feature "partial

extraction" in said claim has to be understood as a specific step directed to the purposive partial extraction of antithrombin.

10.1.3 The Board is therefore not convinced by the argument of the appellant-opponent that the skilled person would consider a standard plasma fractionation process, such as the Cohn process disclosed in D11, as necessarily falling under the scope of claim 1, merely because some antithrombin depletion occurs during the various fractionation steps. Even if, as underlined by the appellant-opponent, the purpose of the Cohn process is generally to remove other plasma proteins (see D11, page 82, 2nd column), it does not contain any step specifically directed to antithrombin partial extraction.

10.1.4 Furthermore the alternative process disclosed in D11 wherein antithrombin is extracted *via* heparin adsorption chromatography corresponds to a full extraction of antithrombin, as extraction is performed on the totality of the antithrombin containing fraction. The Board cannot thus follow the argument of the appellant-opponent that a removal of 100% of antithrombin would anyway not be achieved even when the totality of the fraction is subjected to antithrombin extraction, so that such a process would also amount to a partial extraction. In any case, the Board observes that there is no indication in D11 that the final albumin solutions obtained after antithrombin extraction *via* heparin adsorption chromatography would contain at least 0.03 mg active antithrombin *per* g of albumin.

10.1.5 Accordingly the subject-matter of claim 1 of auxiliary request 32 is novel over D11.

10.2 Novelty with regard to D8, D9 and D16

The Board observes that the objections of lack of novelty of the appellant-opponent based on D8, D9 and D16 follow the same line of argumentation as the objection *versus* D11. The Board thus reaches the same conclusion that claim 1 of auxiliary request is novel over said documents, for the very same reasons as detailed above under 10.1. The admittance of the objections based on D8, D9 and D16, contested by the appellant-patent proprietor, does consequently not need to be decided upon.

11. Inventive step

11.1 In agreement with both parties, the Board considers D9 to represent the closest prior art.

D9 is a scientific review describing various methods for producing human albumin from human plasma. D9 highlights the developments made in industrial processes for the preparation of albumin solutions since the description of the traditional plasma ethanol cold fractionation by Cohn and colleagues in 1946 (see Figure 1). According to this process albumin is separated from other plasma proteins by subsequent precipitation steps with varying ethanol concentration, pH, temperature and ionic strength (see paragraph bridging pages 888-890). Subsequent developments focused on increasing the purity of albumin solutions and particularly further eliminating contaminants such as PKA, which may cause hypotensive effects and for which the pharmacopeia set maximum permitted concentrations (see paragraph bridging pages 891 and 892, page 892 second column 1st and 2nd paragraphs,

page 893 1st column last paragraph and page 893 2nd column 3rd paragraph). The presence of active antithrombin in albumin solution is not specifically discussed, nor is any partial extraction thereof described.

The appellant-opponent based its assessment of inventive step on the Cohn process as closest prior art embodiment, while the appellant-patent proprietor did not concentrate on one specific process described in D9, rather referring to its overall teaching. The Board is of the opinion that the Cohn process can indeed be considered to represent the closest prior art embodiment, because it achieves at least to some extent the same purpose as the presently claimed process (see below 11.3).

11.2 The presently claimed process aims at reducing and stabilising over time PKA activity by maintaining some active antithrombin in the albumin solution thanks to a partial extraction thereof (see for example paragraph [0009] of the patent in suit). According to the appellant-patent proprietor active antithrombin would thus also reduce the formation of PKA from factor XII. The difference between the process of claim 1 of auxiliary request 32 and the Cohn process of D9 is the partial extraction of antithrombin. No purposive antithrombin extraction step is indeed performed in the Cohn process, as previously discussed when assessing novelty.

11.3 As argued by the appellant-opponent, the processes 1-2 of the example of the patent in suit (see Table 2 and paragraphs [0018]-[0019]) correspond to a cold ethanol plasma fractionation process wherein no extraction of active antithrombin was performed on the supernatant of

fractions II+III. These processes do thus correspond to the Cohn process (see also D36 paragraph 35). This was not disputed by the appellant-patent proprietor.
The processes 3-6 of the example of the patent in suit (see Table 2 and paragraphs [0018]-[0019]) correspond to processes wherein 50 or 80% by volume of the supernatant of fractions II+III were subjected to active antithrombin extraction, thus processes wherein a partial extraction was performed according to the present claims. The two last comparative processes reported in table 2 of the patent in suit (see processes 7-8) correspond to processes wherein the totality (100%) of the supernatant of fractions II+III was subjected to active antithrombin extraction. The Board agrees with the appellant-patent proprietor that the processes 3-6, which are in accordance with claim 1, lead to reduced and stabilised PKA activity compared to these last processes 7-8. However, when compared to the processes 1-2 of table 2, which correspond to the prior art Cohn process, no improvement in terms of reduction and stabilisation of PKA activity can be observed. Indeed processes 1-2 contain more active antithrombin and achieve thus the same (if not a better) effect in terms of PKA activity inhibition than the processes 3-6 according to the invention. The Board therefore considers that no particular effect attributable to the distinguishing feature *versus* the closest prior art embodiment has been substantiated.

The disclosure in D8 of an albumin solution (namely 5% NSA) obtained "totally by Cohn fractionation" and potentially containing higher amounts of PKA in the final solution (see table 1 of D8), referred to by the appellant-patent proprietor, does not change this conclusion. No information as to antithrombin content is provided in D8 nor any detailed data regarding the

PKA content (table 1 only provides a range of "<1-38.3 IU/mL"). D8 is therefore not suited to substantiate any effect of a partial active antithrombin extraction in comparison to the Cohn process.

11.4 It follows that, starting from the Cohn process described in D9, the objective technical problem to be solved by the process of claim 1 of auxiliary request 32 is the provision of an alternative process for the production of albumin solutions by plasma fractionation.

11.5 The Board considers that this problem has been solved by the claimed process as revealed by the results of table 2 of the patent in suit. In this context the Board notes that the effect in terms of reduction and stabilisation of PKA activity is a functional feature of the claims, so that solutions not achieving said effect are excluded from the scope of the claims. The issue of achievement of the effect over the entire breadth of the claims raised the appellant-opponent is an issue relevant to sufficiency of disclosure.

11.6 As explained above (see 11.1), D9 generally teaches to eliminate the presence of contaminants, including PKA, to avoid adverse reactions upon treatment with albumin solutions. D9 does not contain any teaching to incorporate an inhibitor of PKA activity and of its formation, let alone antithrombin, to reduce its adverse effects.

The appellant-opponent argued that it would be common general knowledge for the skilled person that protease inhibitors may be used during protein purification to avoid proteolytic degradation and referred to D13 page 184, lines 12-14. As active antithrombin is known to

inhibit PKA and kalikrein activity as shown by D10 (see in particular Chapter 16 and figure 16.1) or D20 (see summary and Figures 1-3), the appellant-opponent concluded that the conservation of some active antithrombin in the albumin solutions would be an arbitrary solution for the skilled person.

The Board cannot share this conclusion, as it appears to be based on hindsight. None of the documents cited by the appellant-opponent refer to the preparation of albumin. In particular, D13 refers neither to albumin nor antithrombin and PKA. D10 and D20 on the other hand relate to blood coagulation mechanisms and in particular to the action of antithrombin III (active antithrombin) on factor XII and PKA. Neither D10 nor D20 is concerned with the preparation of albumin solutions. Hence, the Board considers that there is no hint in said prior art documents to specifically perform partial antithrombin extraction during albumin solutions preparation so as to solve the problem posed. While, as demonstrated by the appellant-opponent, the skilled person could have identified that active antithrombin would inhibit PKA activity, there is no incentive in said prior art documents that would have prompted the skilled person to perform a partial active antithrombin extraction so as to maintain at least 0.03 mg thereof *per* g of albumin in the final albumin solutions instead of following the general trend of increasing albumin solution purity by further removing plasma proteins (*i.e.* including active antithrombin) and contaminants, in partcular PKA.

In relation to the further argument of the appellant-opponent that "abandonning" PKA elimination and "introducing" a PKA inhibitor would be an unnecessary detour in view of the prior art and would thus not

involve an inventive step, the Board is of the opinion that the fact that the alternative solution offered in the present claims might appear *a priori* more cumbersome does not necessarily deprive it of inventiveness. The present process, for the reasons stated above, solves the problem posed and is not suggested by the prior art, which is, in the present case, sufficient to render it inventive.

11.7 Accordingly, the subject-matter of claim 1 of auxiliary request 32 involves an inventive step.

Order

For these reasons it is decided that:

1. The appeals are dismissed.
2. The request for reimbursement of the appeal fee is refused.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated