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Datasheet for the decision of 14 July 2016

Case Number: T 0598/13 - 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

Relevant legal provisions:
EPC Art. 114, 111(1)
RPBA Art. 12(1), 12(4), 13(1), 13(3)

Keyword:
Evidence submitted in appeal proceedings - admitted (yes)
Appeal decision - remittal to the department of first instance (yes)

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Case Number: T 0598/13 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 July 2016

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)
Respondent: (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)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 3 January 2013 rejecting the opposition filed against European patent No. 1656954 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	D. T. Keeling

Summary of Facts and Submissions

I. European patent No. 1 656 954, based on European patent application No. 05380116.3, was granted on the basis of 10 claims.

Independent claims 1 and 9 of the patent 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. The patent was opposed under Article 100(a),(b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed. The following documents were among those cited during the opposition proceedings:

D3: Delivery note No. 80100508 for "Humanalbumin 20% 50 ml" delivered to P.N. Gerolymatos S.A.
D9: British Journal of Anaestesia 85(6), 887-895, 2000
D14: Declaration of Dr Freudenberg
D15: Declaration of Mr Moses

III. By decision posted on 3 January 2013 the opposition division rejected the opposition. The opposition division came, *inter alia*, to the following conclusions:

(a) The late-submitted documents D14 and D15 were admissible in that they were filed by the opponent to answer questions raised by the opposition division in the preliminary opinion.

(b) When the invention was conceived, the person skilled in the art would have been able to determine whether a sample of antithrombin was active or not. The requirement of sufficiency of disclosure was therefore met.

(c) It appeared credible that the product "Humanalbumin 20% 50 ML" with batch number 12644431C was made available to the public before the priority date of the patent despite some inconsistency in D3 concerning the quantity of the product delivered. However, a clear indication of the amount of active antithrombin contained in the product at the time it was made available to the public was missing. Hence, it was not proved beyond any reasonable doubt that the product available to the public had a composition included in the scope of claim 9. The subject-matter of the patent was novel also over the other documents mentioned by the opponent in relation to the requirement of novelty.

(d) Document D9 was the closest prior art for the assessment of inventive step. The albumin solution of the opposed patent differed from the albumin of D9 in the presence of PKA and in the partial elimination of antithrombin. The objective

technical problem was to be seen in the provision of a "human albumin solution with an alternative solution to avoid hypotension". The skilled person was aware that PKA could cause hypotension. The prior art did not suggest introducing a PKA-inhibitor in the albumin solution instead of removing the PKA during the preparation in order to avoid hypotension. The subject-matter of claims 1 to 10 was therefore inventive.

IV. The opponent (hereinafter appellant) lodged an appeal against that decision.

With the statement setting out the grounds of appeal filed on 13 May 2013 the appellant submitted the following pieces of evidence:

D18: JBC, 251(21), 6481-6488, 1976
D19: JBC, 257(4), 1779-1784, 1982
D20: Biophysical research communication 74(1), 150-158, 1977
D21: 2nd Declaration of Michael Moses

V. By letter dated 13 September 2013 the patent proprietor (hereinafter respondent) requested that the appeal be dismissed and that the patent be maintained as granted, or alternatively that the patent be maintained on the basis of auxiliary requests 1, 1A and 2 to 6 submitted with the same letter.

The respondent also submitted the following documents with the reply to the appeal:

D23: Proof of albumin content in the patentee's commercial products

D24: Excerpt from the European Pharmacopoeia, 4th Edition, 2001

VI. In a communication pursuant to Article 15(1) RPBA issued on 13 May 2016, the Board made *inter alia* the following considerations:

(a) As noted by the opposition division, the gross weight of the product "Human albumin 20% Behring" with batch number 12644431C and the volume reported in the first page of D3 did not match with the data disclosed in page 2 of the same document. This issue needed to be considered during the oral proceedings.

(b) The term "stability" was used in the patent in suit in relation to the PKA activity. The experimental data disclosed in Table 2 of the patent concerning the stability of the human albumin solution were to be considered during the oral proceedings in relation to the requirement of sufficiency of disclosure. In discussing whether the albumin solutions of the patent were stable over time, it was important to take into account that claim 9 covered also compositions in which the extraction was close to 100%.

(c) Two different conversion factors could be used to calculate the amount of active antithrombin in the units used in the claim starting from the value in IU/ml. The skilled person faced with the problem of reproducing an invention disclosed in a patent filed in 2004, would have very likely decided to use the conversion factor disclosed in D10 published in 2001 rather than the conversion factor disclosed in D17 published in 1983.

VII. Additional documents were submitted by the appellant with letters of 14 June 2016 (documents D25 and D26) and 7 July 2016 (documents D27 to D30):

D25: Declaration of Günter Vollmer
D26: Clinical methods: the history, physical and laboratory examination, 3rd edition (1990), chapter 101, Serum albumin and globulin
D27: The biology of antithrombins, CRC, 1990, page 50
D28: Blood coagulation, biochemistry (Mosc.), 2002, 67(1), 3-12
D29: Drugs and laboratory parameters, 1st edition, September 2010, 34
D30:Grifols Thrombate III product info, August 2013

VIII. By letter dated 14 June 2016 the respondent submitted four additional auxiliary requests designated 3a to 3d. The following document was submitted by the respondent on 11 July 2016:

D31: Human blood plasma proteins: structure and function, 2008, p.288 and 301

IX. Oral proceedings were held on 14 July 2016.

X. The appellants' arguments, as far as they are relevant for the present decision, can be summarised as follows:

(a) Documents D18 to D21 were filed in response to arguments of the respondents or to considerations made by the opposition division in the appealed decision. Document D25 was filed in response to the communication issued by the Board. Documents D26 to D30 reflected the common general knowledge at the priority date and were relevant for the assessment

of the sufficiency of disclosure. All these documents were to be admitted into the appeal proceedings.

(b) Remitting the case to the department of first instance was against the need for procedural economy and did not appear necessary since the Board could figure out the position of the opposition division in relation to the issues of sufficiency. In any case, there was nothing to prevent the Board from deciding on the other grounds of opposition before remitting the case.

XI. The appellants' arguments, as far as they are relevant for the present decision, can be summarised as follows:

(a) Documents D14 and D15 were not *prima facie* relevant. In admitting these documents, the opposition division did not exercise its discretion under Article 114 EPC in a reasonable way. Hence, documents D14 and D15 were to be excluded from the appeal proceedings.

The appeal proceedings were conceived as a judicial review of a separate first instance decision.The assessment of the correctness of a first instance decision was to be based on facts, evidence and arguments which were already known to the department of first instance. Accordingly, documents D18 to D21 and D25 to D30 were not to be admitted into the appeal proceedings.

Moreover, documents D18 to D20 were published well before the priority date of the patent. Hence, these documents could have been submitted earlier. The same held true for the experimental report D21

which related to objections already raised in the notice of opposition and for documents D27 to D30 which concerned the concentration of antithrombin in human plasma, a topic which had been discussed since the beginning of the opposition proceedings.

(b) If documents D18 to D21 and D27 to D30 were admitted into the proceedings the case was to be remitted to the department of first instance to give the respondent the opportunity to defend its position before two instances.

XII. The appellant requested that the decision under appeal be set aside and that the patent be revoked. The appellant requested further that auxiliary requests 1, 1a, 2 and 3 not be admitted into the proceedings.

XIII. The respondent requested that the appeal be dismissed and the patent maintained as granted (main request) or, in the alternative, that the patent be maintained on the basis of one of the auxiliary requests filed by letter of 13 September 2013 (namely, auxiliary requests 1, 1a, 2, 3, 4, 5 and 6) or by letter of 14 June 2016 (namely, auxiliary requests 3a, 3b 3c and 3d). The respondent requested further that documents D14, D15, D18 to D21 and D25 to D30 not be admitted into the proceedings; further, if documents D18 to D21 and D27 to D30 were to be admitted into the proceedings, that the case be remitted to the opposition division for further prosecution.

Reasons for the Decision

1. Admittance of documents

1.1 Documents D14 and D15

Documents D14 and D15 were admitted by the opposition division into the opposition proceedings and therefore form part of the basis of the appeal proceedings pursuant to Article 12(1) and (4) RPBA.

In the appealed decision it is explained that the submission of documents D14 and D15 was regarded as a reaction of the opponent to some considerations set out by the opposition division in the preliminary opinion in relation to the prior use. In the Board's view, the opposition division did not exercise its discretion under Article 114 EPC in an unreasonable way. Hence, the Board sees no reason to overrule the decision to admit documents D14 and D15.

1.2 Documents D18 to D21

These documents were submitted by the appellant with the statement setting out the grounds of appeal. Accordingly, they form part of the basis of the appeal proceedings pursuant to Article 12(1) RPBA and they can be held inadmissible in accordance with Article 12(4) RPBA only if they could have been presented in the first instance proceedings.

1.2.1 Documents D18, D19 and D20 have been submitted by the appellant to support its arguments in relation to inventive step. In particular these documents discuss the effects of antithrombin on factor XIIa (PKA), whose presence in human albumin may cause hypotension (see

[0003] of the patent). The submission of D18 to D20 appears therefore to address the conclusion of the opposition division as to the absence of documents suggesting antithrombin as a means to avoid hypotension (see point III(d) above).

In the Board's view there were no compelling reasons for the appellant to file these documents during the first instance proceedings.

1.2.2 Document D21 is an experimental report submitted by the appellant in relation to the discussion on the sufficiency of disclosure. It provides *inter alia* data on the content of active antithrombin in human albumin samples obtained by a process according to the patent. From points II.5.1) and II.5.2) of the appealed decision and from point 4 of the minutes, it appears that it was a matter of dispute between the parties during the first instance proceedings whether the antithrombin contained in the albumin was entirely active, as maintained by respondent, or whether also non-active anti-thrombin was present as argued by the appellant. The main argument of the respondent in this regard was that the appellant had the burden to prove its allegation. The experiments of document D21 address this issue. Thus, by filing document D21 the appellant is reinforcing a line of attack already taken before the first instance. This is to be regarded as a normal behaviour of a losing party.

The Board also considers that the situation during the first instance proceeding was not such that the filing of document D21 should have taken place already at that stage.

1.3 Documents D25 to D30

These documents were submitted by the appellant with letters of 14 June 2016 (D25 and D26) and 07 July 2016 (D27 to D30). The admittance of these documents into the appeal proceedings is therefore to be considered under the provisions of Article 13(1) and (3) RPBA. Additionally, also 12(4) RPBA applies.

1.3.1 Document D25 is a declaration of an employee of the appellant which has been filed in order to clarify some inconsistency noted by the Board in relation to the content of document D3 (see point VI(a) above).

D26 is an article providing the information that the content of albumin in human serum varies within the range 3.5-5.0 g/dl.

Documents D27 to D30 address some considerations made by the Board in its communication in relation to the factor for converting the units IU/ml into the units mg/g (see point VI(c) above). The data disclosed in these documents suggest that other conversion factors could be used in addition to the one disclosed in D10.

Thus, documents D25 and D27 to D30 have been filed by the appellant as a direct reply to the considerations made by the Board in its communication pursuant to Article 15(1) RPBA. D26 illustrates the common general knowledge at the priority date. All these documents are potentially relevant in particular in relation to issues concerning the requirement of sufficiency of disclosure (see also point 2 below). Furthermore, in the Board's view there is no reason to consider that these documents should have been filed already during the first instance proceedings.

1.4 The Board agrees with the respondent that the primary function of the appeal proceedings is to give a judicial decision on the correctness of a decision of a department of first instance. However, that does not imply that evidence submitted for the first time on appeal is automatically inadmissible. A rigid rule excluding all new evidence on appeal might lead to injustice and unfairness in some cases and would not be compatible with the principles of procedural law generally recognized in the Contracting States (Case Law of the Boards of Appeal of the EPO, 8th Edition 2016, IV.C.1.1.1).

The admittance of the new items of evidence filed during the appeal proceedings is assessed in the light of Articles 12 and 13 of the Rules of Procedure of the Boards of Appeal with due regard to the criteria established by the case law of the Boards of Appeal. Aspects that the Board may consider in the exercise of its discretion include the relevance of the new evidence and whether this was submitted as a legitimate reaction to the first-instance decision (Case Law of the Boards of Appeal of the EPO, 8th Edition 2016, IV.C.1.3)

In line with these general directions the Board decides to admit into the appeal proceedings documents D18 to D21 and D25 to D30.

1.5 No objections have been raised by the appellant against the admittance of the documents submitted by the respondent during the appeal proceedings, namely document D23, D24 and D31.

Documents D23 and D24 have been filed by the respondent with the reply to the appeal and therefore form part of the basis of the appeal proceedings pursuant to Article 12(1) RPBA. The Board sees no reason why these documents should not be admitted into the appeal proceedings.

Document D31 was submitted by the respondent on 11 July 2016 in response to the filing of documents D27 to D30. Also D31 contains relevant information in relation to the factor for converting the units IU/ml into the units mg/g.

Thus, documents D23, D24 and D31 are also admitted into the appeal proceedings.

2. Main request (patent as granted) - Sufficiency of disclosure

2.1 In independent claims 1 and 9 the amount of active antithrombin in the final purified human albumin solution is expressed in milligram per gram of albumin (mg/g of albumin). The main point addressed in the appealed decision in relation to the requirement of sufficiency of disclosure is whether the skilled person would have been able to measure the amount of active antithrombin in these units based on the information disclosed in the patent and on his general knowledge. The opposition division came to the conclusion that at the time the invention was conceived means existed for the skilled person to make such a measurement. In this respect it was immaterial that the amount of active antithrombin was expressed in mg/g instead of the commonly used units IU/ml.

2.2 It is uncontested by the parties that the skilled person knew at the filing date of the patent how to measure the antithrombin activity in IU/ml. The chapter "Assay of human antithrombin III" of D24 provides evidence of this. It is also undisputed that the measurement in IU/ml can be converted into the units used in the patent by using a conversion factor, corresponding to the normal concentration of antithrombin in human plasma.

In the respondent's opinion, the skilled person would therefore easily obtain the amount of active antithrombin in mg/g by applying to the value in IU/ml the conversion factor disclosed in D10 (1 IU = 140 µg).

With the statement setting out the grounds of appeal the appellant argued that documents D10 and D17 disclosed two different conversion factors which, applied to the same value of active antithrombin expressed in IU/ml, gave different values in the unit mg/g.

In its communication of 13 May 2016 (see point VI(c) above) the Board, in agreement with the respondent's position, expressed the view that the skilled person faced with the problem of reproducing an invention disclosed in a patent filed in 2004, would have very likely decided to use the conversion factor disclosed in D10 published in 2001 rather than the conversion factor disclosed in D17 published in 1983.

2.3 In reply to the Board's communication the appellant submitted documents D27 to D30. In response to this the respondent filed document D31. All these documents provide data as to the concentration of antithrombin in human plasma. The data are quite divergent thereby

leading to different conversion factors. In the Board's view particularly relevant are the data disclosed in documents D27 and D28 which were published before the filing date of the patent in suit. According to D27, published in 1990, the antithrombin concentration in human plasma varies between 0.10 and 0.42 g/l (page 50, section "B. Normal value of AT-III). According to D28, published in 2002, the mean plasma concentration of antithrombin is 200 µg/ml (page 4, Table 1).

2.4 The opposition division considered in its decision that the skilled person was able at the filing date of the patent to determine the amount of active antithrombin and that it was not relevant in the context of assessing sufficiency of disclosure that the amount of antithrombin was expressed in mg/g.

In the light of the considerations set out above, it appears that if the value of active antithrombin in the units expressed in the claims is obtained by converting the amount determined in IU/ml, then different values may be obtained depending on the conversion factor used.

This issue needs therefore further consideration in the light of the documents submitted during the appeal proceedings. In the same context it appears important also to consider whether any issue arising from the use of the units mg/g for the amount of active antithrombin should be regarded as a potential problem of sufficiency of disclosure or whether it should be regarded as an issue pertaining to the clarity of the claims. The decision of the opposition division does not reveal whether this aspect was considered during the first instance proceedings.

2.5 A further relevant issue concerning the requirement of sufficiency of disclosure is whether the skilled person would be able to prepare a purified human albumin having an active antithrombin content in the ranges defined in claims 1 and 9. This issue is of paramount importance because it directly relates to the question whether the skilled person is able to perform the process defined in claim 1 or to obtain the product defined in claim 9.

The experimental report D21 submitted by the appellant with the statement setting out the grounds of appeal addresses this issue. The report discloses some analytical data relating *inter alia* to a sample of human albumin prepared by a process involving the partial extraction of antithrombin. According to the indications provided in the second and third paragraph of page 3 of D21, this process should correspond to the process of the patent in suit. The results disclosed in the table of page 5 of D21 indicate that the amount of active antithrombin in a sample obtained after partial extraction (66%) is 0.01 mg/g of albumin, i.e. outside the ranges defined in claims 1 and 9. According to the conclusions of the author of the experiments of D21, the amount of of active antithrombin is below the value of 0.03 mg/g of albumin defined in claim 1 even when no antithrombin extraction occurs.

The results of the experimental report D21 have been contested by the respondent.

As mentioned above, the experiments of D21 directly address the question of whether the skilled person would be able to perform the invention defined in claims 1 and 9 on the basis on the information disclosed in the patent. These experiments are

therefore potentially highly relevant in the context of assessing the requirement of sufficiency of disclosure.

Thus, the Board considers that the issues arising from the submission of document D21 need further investigation.

2.6 In the statement setting out the grounds of appeal the appellant raised some objections concerning the sufficiency of disclosure of claims 1 and 9 in relation to the features "stabilizing over time" (claim 1) and "stability over time" (claim 9).

This issue was not considered in the appealed decision.

The Board notes that the effect concerning the stability over time is expressed in claims 1 and 9. Hence, assessing whether this effect is achieved across the scope of the claims is a matter concerning the sufficiency of disclosure (see G1/03, OJ 2004, 413, point 2.5.2 of the reasons).

2.6.1 As indicated in the communication on 13 May 2016 (see point VI(b) above), it is clear in the Board's opinion that the term "stability" is used in the patent in suit in relation to the PKA activity. This emerges for instance from paragraph [0008] of the description or from the feature "stabilizing it over time" of claim 1, wherein the word "it" refers to the PKA activity.

It furthermore appears from the observations made in paragraph [0019] of the patent in suit, that the albumin solutions obtained in the processes 7 and 8 of Table 2 are not regarded as stable in terms of PKA activity. Processes 7 and 8 are characterized by a complete extraction of the antithrombin. Conversely, in

the albumin solutions obtained in the processes 1 to 6 in which no antithrombin extraction or only partial antithrombin extraction occurs, the PKA activity remains low. Thus, even in the absence of a precise definition of the concept of "stability over time" the whole teaching of the patent and in particular paragraph [0019] makes it possible to distinguish "stable" solutions (processes 1 to 6) from "non-stable" solutions (processes 7 and 8).

In the Board's opinion, in deciding whether the albumin solutions of the patent are stable over time, it should be considered that the claims cover processes in which the extraction is close to 100% and products obtained by these processes.

Since during the first instance proceedings this aspect of the sufficiency of disclosure was apparently not dealt with, also in this respect a further investigation of the ground of opposition under Article 100(b) EPC appears necessary.

3. Remittal

3.1 In order to decide on the ground of sufficiency of disclosure the Board would need to consider all the issues presented in point 2 above. However, as it emerges from the previous paragraphs, these issues are based also on evidence and arguments which have been presented for the first time in appeal proceedings. Thus, a complete assessment of the requirement of sufficiency of disclosure did not take place during the first instance proceedings.

Under these circumstances the Board consider it appropriate to remit the case to the department of

first instance for a substantive examination of the ground pursuant to Article 100(b) EPC, in particular in relation to the issues discussed under point 2 above (Article 111(1) EPC).

3.2 The appellant expressed the view that the case should not be remitted to the department of first instance. In this respect it argued *inter alia* that the Board could figure out the opposition division's position in relation to certain issues such as the conversion of the units IU/ml into the units mg/g. It furthermore observed that remitting the case for further prosecution was against the principle of procedural economy.

3.3 As to the first argument, the Board observes that the impugned decision does not provide any clear hint that could be used to figure out how the opposition division would decide on the various issues discussed above. The Board cannot even anticipate whether the question concerning the units used for expressing the amount of active antithrombin will be regarded by the opposition division as a matter pertaining to the sufficiency of disclosure or rather to the clarity of the claims. It would therefore be inappropriate for the Board to embark on speculative considerations as to the position of the opposition division on the various issues.

As to the need for procedural economy, the Board is of course aware that a remittal results in a prolongation of the proceedings. However, the length of the proceedings is also influenced by the behaviour of the parties. In particular, the filing of new evidence in the course of the appeal proceedings may prompt the Board to remit the case to the department of the first instance for various reasons, for instance because a

fresh case is created by the new evidence or to give the parties an adequate opportunity to defend their cases before two instances. Thus, a party submitting new evidence in the course of appeal proceedings should be aware of the possible consequences of this.

3.4 The appellant also requested the Board to decide on the other grounds of opposition.

However, the Board can neither anticipate the conclusions of the opposition division in relation to the sufficiency of disclosure nor any possible reaction of the parties, including the filing of new sets of claims from the side of the respondent. Thus, the Board considers it appropriate to refrain from taking partial decisions that may potentially have an impact on the further prosecution of the case.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Opposition Division for further prosecution.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated