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# D E C I S I O N
## of 21 February 2001

**Case Number:** T 0526/97 - 3.3.2

**Application Number:** 90100474.7

**Publication Number:** 0378208

**IPC:** A61L 2/00

**Language of the proceedings:** EN

**Title of invention:**
Production method for protein-containing composition

**Appellant:**
Welfide Corporation

**Opponent:**
HemaSure A/S

**Headword:**
Virus inactivation/WELFIDE

**Relevant legal provisions:**
EPC Art. 56, 114, 123
EPC R. 55(c), 56(1)

**Keyword:**
"Admissibility of the opposition on the ground of lack of novelty (yes): notice of opposition complies with the requirements of Rule 55(c)"
"Admissibility of late-filed pieces of prior art"
"Main and first auxiliary requests, inventive step (no)"
Second auxiliary request, inventive step (yes)"

**Decisions cited:**
T 0182/89

**Catchword:**
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0526/97 - 3.3.2

# D E C I S I O N
## of the Technical Board of Appeal 3.3.2
## of 21 February 2001

**Appellant:** (Proprietor of the patent)
Welfide Corporation
6-9, Hiranomachi 2-chome
Chuo-ku
Osaka (JP)

**Representative:**
von Kreisler, Alek, Dipl.-Chem.
Patentanwälte
von Kreisler-Selting-Werner
Postfach 10 22 41
D-50462 Köln (DE)

**Respondent:** (Opponent)
HemaSure A/S
Sauntesvej 13
2820 Gentofte (DK)

**Representative:**
Christiansen, Ejvind
Hofman-Bang A/S
Hans Bekkevolds Allé 7
2900 Hellerup (DK)

**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 21 March 1997 revoking European patent No. 0 378 208 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** P. A. M. Lançon
**Members:** G. F. E. Rampold
S. U. Hoffmann

## Summary of Facts and Submissions

I. The appellant is proprietor of European patent No. 0 378 208 (application No. 90 100 474.7). Claim 1 as granted reads as follows:

"A method for preparing a virus-inactivated protein-containing composition, comprising the steps of:

(a) contacting a protein-containing liquid composition which may be contaminated with virus with a trialkyl phosphate;
(b) removing the trialkyl phosphate from the protein-containing liquid composition;
(c) lyophilizing the protein-containing liquid composition to obtain a dry protein-containing composition; and
(d) heat-treating the dry protein-containing composition."

Dependent claims 2 to 8 relate to specific elaborations of the method according to claim 1.

II. The respondent (opponent) filed a notice of opposition to the grant of the patent requesting its revocation under Article 100(a) EPC on the grounds of lack of novelty and inventive step.

III. The following citations submitted in support of the opposition remain relevant to the present appeal:

(1) K. Wallevik et al, "Purification oh high purity FVIII Coagulation Protein at a yield of 40% by a three step temperature dependent Purification from

heparinized Plasma" published in Biotechnologie des protéines du plasma, J. F. Stoltz, C. Rivat Eds. Colloque INSERM, Vol. 175, 1989, pages 287 to 294;

(2) US-A-4 540 573;

(6) EP-A-0 142 059;

(8) WO 82/03871;

(9A) P. P. Mortimer,"Parvovirus B19 and Blood Transfusion", The XX Congress of the International Society of Blood Transfusion, Educational Book, 1988, page 27;

(9B) P. P. Mortimer et al, "Transmission of Parvovirus B19 by Factor Concentrate", The XX Congress of the International Society of Blood Transfusion, Book of Abstracts 1988, page 272;

(10) G. A. Rock et al, "Stability of VIII:C in Plasma: The Dependence of Protease Activity and Calcium", Thrombosis Research 29; pages 521 to 535, 1983;

(11) J. K. Smith, "Preparation and Safety of Fractionated Plasma Products", The XX Congress of the International Society of Blood Transfusion, Educational Book, 1988, pages 80 to 92.

IV. The patent was revoked pursuant to Article 102(1) EPC by a decision of the opposition division posted on 21 March 1997. The stated ground for the revocation was lack of novelty of the claim 1 as granted (main

request) and lack of inventive step of all three auxiliary requests filed in the course of the first-instance opposition proceedings. The essence of the reasoning in the opposition division's decision was as follows:

Citation (1), although published after the first priority date of the patent in suit (13 January 1989), had to be considered as a true and authentic account of an earlier oral presentation delivered by the principal author of (1), K. Wallevik, at the "INSERM symposium" in May 1988 (hereinafter referred to as "symposium"). The content of (1) constituted thus prior art within the meaning of Article 54(2) EPC. Since citation (1) referred to a method for preparing a virus-inactivated factor VIII coagulation protein, comprising all four steps (a) to (d) according to claim 1 of the contested patent, its disclosure was prejudicial to the novelty of the main request.

Claim 1 of the first auxiliary request differed from claim 1 of the main request by explicitly requiring the inactivation of both enveloped (lipid-coated) and non-enveloped viruses. The skilled person following the sequence of steps disclosed in document (1) would necessarily arrive at the required result, because citation (2) described the inactivation of lipid-coated or enveloped viruses in blood products by contacting said products with di- or trialkyl phosphate, preferably in the presence of a detergent [in the following referred to as solvent/detergent (S/D) treatment], and citation (8) the inactivation of both enveloped and non-enveloped viruses by dry heat treatment of the freeze dried products.

Claim 1 of the second and third auxiliary requests included the additional specification that in step (a) of the claimed method the protein composition was brought into contact with trialkyl phosphate in the presence of a protease inhibitor. Since citation (10) suggested the addition of protease inhibitors to improve the stability of blood plasma products during their recovery and storage, the subject-matter of the second and third auxiliary requests was likewise devoid of inventive step.

V. The proprietor of the patent (appellant) lodged an appeal against this decision and filed together with the appeal statement new auxiliary requests I to III.

VI. The respondent's reply to the statement of the grounds of appeal was accompanied by a series of additional citations (12)-(23) and declarations by the principal author of (1), K. Wallevik (24), who also made the oral presentation at the "symposium", and P. Kaersgaard (25), who attended said presentation.

VII. The board issued a communication stating its reservations under the terms of Rule 57(a) EPC as to the admissibility of the appellant's auxiliary requests filed with the statement of the grounds of appeal. About one month in advance of the oral proceedings, scheduled to take place on 21 February 2001, the appellant submitted in reply to the board's communication amended auxiliary requests I to III to replace all the previously presented auxiliary requests.

The differences between the respective claim 1 of the current first and second auxiliary requests and claim 1

as granted are set out below, with additions in steps (a) and (b) being indicated in bold italic letters and the introductory portion of the claim and steps (c) and (d) remaining the same;

**first auxiliary request:**

"(a) contacting a protein-containing liquid composition which may be contaminated with virus with a trialkyl phosphate ***in the presence of a surfactant;***

(b) removing the trialkyl phosphate ***and the surfactant*** from the protein-containing liquid composition";

**second auxiliary request:**

"(a) contacting a protein-containing liquid composition which may be contaminated with virus with a trialkyl phosphate ***in the presence of a protease inhibitor***;

(b) removing the trialkyl phosphate ***and the protease inhibitor*** from the protein-containing liquid composition."

VIII. Shortly before the oral proceedings the respondent submitted the following additional pieces of evidence:

(26) L. Winkelman et al, "Treatment of a new high specific activity factor VIII concentrate to inactive viruses", Thrombosis and Haemostasis, No. 1, Vol. 54, 1985, page 19;

(27) declaration by J. Ingerslev, who is a co-author of

(1).

IX. The appellant’s arguments submitted in writing and during the oral proceedings can be summarised as follows:

The pieces of evidence, which were presented by the respondent for the first time after the nine-month opposition period had expired, were filed late and out of time and should therefore not be admitted into the proceedings.

The opposition on the ground of lack of novelty was based solely on the disclosure of citation (1). However, the burden of proof remained on the respondent in his role as an opponent to prove that citation (1) represented a true and authentic account of the earlier oral disclosure during the "symposium". Since the respondent had failed to provide such proof in his notice of opposition, the opposition on the alleged ground of lack of novelty was not *per se* properly supported as required by Rule 55(c) EPC within the nine-month period for opposition and should, accordingly, be rejected as being inadmissible pursuant to Rule 56(1) EPC, in accordance with the ruling of decision T 182/89 (OJ EPO 1991, 391).

Even if the board were to accept - for the sake of argument and for the respondent's benefit - that the disclosure of citation (1) formed part of the state of the art under Article 54(2) EPC, this would not affect the novelty and inventive step of the claimed method in the patent in suit. Citation (1) referred in the context of the inactivation of viruses in labile blood derivatives either to S/D treatment of factor VIII,

with tri-n-butyl phosphate (TNBP) being the solvent, on the one hand, or to dry heat treatment, on the other, as strictly alternative methods, but did not disclose their combination in one single method of virus inactivation. Thus, citation (1) in fact taught away from the concept of combining S/D treatment and dry heat treatment for the inactivation of viruses in protein-containing products.

Citation (2) suggested indeed in mere general terms the possibility of combining S/D treatment, which was known to be suitable for the inactivation of lipid-coated or enveloped viruses only, with still other methods of inactivating viruses, including those for non-enveloped viruses. However, the respondent, trying to combine the teaching of citations (1) or (2) with that of references (6), (8) or (26) failed to demonstrate why the skilled man, faced with the problem of providing a method of inactivating both enveloped and non-enveloped viruses, was invited to combine any of the above cited references, as none of them referred to the capability or use of dry heat treatment specifically for the inactivation of non-enveloped viruses.

Citation (10) merely contained a general reference to the use of protease inhibitors for the stabilisation of plasma proteins during their recovery and storage, but was entirely silent about the use of a protease inhibitor during S/D treatment of proteins with di- or trialkyl phosphate. This being the case, the skilled man had no reason to combine the teaching of (1), (2) or (6) with that of (10) with a reasonable expectation of success.

X. The respondent disagreed relying essentially on the

following arguments:

The declarations by K. Wallevik (24) in conjunction with those by P. Kaersgaard (25) and J. Ingerslev (27) provided satisfactory proof of the respondent's submission that all the essential details of the method for the purification and virus inactivation of factor VIII described in (1), including the treatment of purified factor VIII with TNBP and the subsequent heat treatment of the lyophilized concentrate, had been subject of Dr Wallevik's oral presentation at the "symposium".

Notwithstanding the disclosure of document (1), prior to the priority date of the patent in suit it was well established in the state of the art that S/D treatment, with TNBP being the solvent, was effective in the inactivation of enveloped viruses, but did not inactivate non-enveloped viruses, while dry heat treatment of proteins was effective in the inactivation of both enveloped and non-enveloped viruses. In particular citations (2) and (11) already suggested to the skilled person the combination of S/D treatment and heat treatment to achieve an increasingly effective inactivation of both enveloped and non-enveloped viruses. It was, moreover, well established in the state of the art, that heat treatment of plasma proteins in a water-free or substantially water-free dry condition resulted in prevention, at least to a significant extent, of loss in the protein's specific activity as compared with heat treatment in the liquid-phase. Further, the skilled man would have known from citation (8) that dry heat treatment was preferentially employed for the virus-inactivation of non-enveloped or, differently expressed, non lipid-coated viruses.

Consequently, the skilled person seeking in the state of the art a suitable method for an improved and increasingly effective inactivation of both enveloped and non-enveloped viruses in protein-containing products, without substantially impairing the protein's activity, and being aware of the factual ineffectiveness of TNBP in the activation of non-enveloped viruses would necessarily arrive at the combination suggested in the patent in suit, comprising the combination of S/D treatment using TNBP and dry heat treatment.

The use of a protease inhibitor in all modes of recovery and virus-deactivation of labile protein derivatives was derivable for a person skilled in the art from the teaching of citation (10) and a number of other citations filed in the course of the appeal proceedings. The appellant failed to provide a good argument or a technical reason why the skilled person would not have used a protease inhibitor in the S/D treatment according to step (a) of the claimed method of virus-inactivation as well.

XI. The appellant requests that the decision under appeal be set aside and the patent be maintained unamended or in amended form on the basis of one of the auxiliary requests I to III, submitted on 23 January 2001 with the appellant's letter dated 22 January 2001.

The respondent requests that the appeal be dismissed.

## Reasons for the Decision

1. The appeal is admissible.

2. The appellant's objection based on Rules 55(c) and 56(1) EPC to the admissibility of the respondent's opposition pursuant to Article 100(a) EPC on the ground of lack of novelty of the subject-matter of claim 1 as granted appears to result from a mistaken interpretation of the conclusions reached in decision T 182/89 (*loc. cit.*). The question as to whether a notice of opposition fulfils the requirements of Rule 55(c) EPC must be distinguished from the question of the strength of the opponent's case.

2.1 The third requirement of Rule 55(c) EPC stipulates that the notice of opposition should contain an indication of the "facts, evidence and arguments" presented in support of the grounds on which the opposition is based.

In the present case the evidence concerned is clearly indicated and specified in the notice of opposition by the following details: the full text of citation (1), the date of its publication and the periodical where it was published; further the exact date and place of the alleged prior oral disclosure of the content of (1); the identification of the person who made the oral presentation and another person attending it.

It is, moreover, clearly stated which alleged facts said evidence is intended to prove in the present case, namely the allegation of lack of novelty of the claimed subject-matter in the patent in suit on the basis of the alleged prior oral disclosure of the content of citation (1).

2.2 It ensues from the above observations that the requirements of Rule 55(c) EPC are clearly met in the respondent's notice of opposition. Assessing the evidence does **not affect the opposition's admissibility**, but is part of the process of ascertaining whether the opposition is well founded in substance. Consequently, there can certainly be no doubt that the opposition under Article 100(a) EPC on the ground of lack of novelty is admissible under the terms of Rule 56(1) EPC.

3. The three sets of claims forming the appellant's current first, second and third auxiliary requests were only received on 23 January 2001, i.e. less than one month before the date set for oral proceedings. These requests could, therefore, be considered late-filed. However, the claims of the appellant's present requests are essentially based on the auxiliary requests filed together with the appeal statement and have admittedly been amended so as to dispel the board's reservations under Rule 57(a) EPC to the admissibility of the previously filed auxiliary requests. Therefore, in the circumstances of the case the board decided during the oral proceedings to admit the main, first and second auxiliary requests for their consideration.

4. In support of his allegation of lack of novelty and inventive step the respondent (opponent) relied in the course of first instance opposition and the opposition appeal proceedings on a series of 27 pieces of evidence which were filed in the following chronological order:

(a) citations (1) to (6): together with the notice of opposition on 28 April 1995;

(b) citations (7), (8), (9A), (9B), (10) and (11): in advance of the oral proceedings before the opposition division on 5 February 1997;

(c) citations (12) to (23); declarations by K. Wallevik (24) and P. Kaersgaard (25): together with the respondent's reply to the statement of the grounds of appeal on 14 May 1998;

(d) citation (26): together with the respondent's letter on 28 December 2000;

(e) declaration by J. Ingerslev (27): together with the respondent's letter on 14 February 2001.

4.1 In view of the appellant's objection to the admissibility of the pieces of evidence filed after expiry of the nine-month opposition period, the question arises whether such evidence should be admitted for consideration in this appeal.

4.2 The group (b) citations referred to above were clearly filed in response to the opposition division's preliminary opinion in its Rule 71a communication indicating that the claimed subject-matter in the patent in suit, if limited to the concurrent inactivation of non-enveloped and enveloped viruses or to a method of inactivating viruses in the presence of a protease inhibitor in step (a), would potentially be patentable. In addition, the group (b) citations were filed during the first-instance opposition proceedings already before the date set for oral proceedings and fall, moreover, within the category of citations which the board considers to be particular relevant to the decision in the present case. In view of the foregoing,

their consideration and admission into the appeal proceedings is fully justified and even necessary from a procedural and legal point of view.

4.3 As has correctly been submitted by the respondent, the group (c) citations were filed directly in response to the observations, arguments and auxiliary requests presented with the statement of the grounds of appeal. This group includes a series of citations which are intended to prove that, contrary to the appellant’s assertion in the appeal statement, at the priority date a final dry heat treatment step was known to be effective in inactivating both enveloped and non-enveloped viruses and, moreover, was conventionally used for the inactivation of viruses in protein-containing compositions. Other citations of this group refer to the use of protease inhibitors in the recovery and purification of plasma proteins and are intended to counter the appellant’s submissions in the statement of the grounds of appeal as to the patentability of the second and third auxiliary requests filed together with the appeal statement. Consequently, the board considers that by filing these citations the respondent reacted as soon as possible and already at an early stage of the appeal proceedings to the appellant's submissions and sees therefore no sound reason why these citations should be disregarded under Article 114(2) EPC.

4.4 By filing the declarations (24), (25) and (27) the respondent apparently sought to reply to the submissions and arguments regarding the non-relevance of citation (1), brought forward by the appellant in the statement of the grounds of appeal and in his letter dated 22 January 2001 respectively. Moreover, the board considers that the said declarations were

referred to by the respondent in support of his prevailing argumentation regarding the relevance of the alleged prior oral disclosure of citation (1) to the present case. Consequently, the declarations are to be regarded as part of these arguments rather than as citations which, under Article 114(2) EPC, could be rejected as being late.

4.5 To the contrary, the respondent submitted citation (26) only on 28 December 2000, ie more than five years after the end of the time limit for opposition, more than three years after the statement setting out the ground of appeal had been filed, and less than two months before the date set for the oral proceedings before the board, without any recognisable reason for such late filing. In spite of the fact that citation (26) appears to represent a highly relevant piece of prior art in respect of the main and first auxiliary requests, the question as of whether or not it should be admitted into the proceedings does not, however, affect the decision in the present case. The main and the first auxiliary requests must in any case fail for the reasons set out below on the basis of the state of the art justifiably admitted into the appeal proceedings. On the other hand, the disclosure of (26) is not relevant in the sense that it would prevent the second auxiliary request being patentable.

5. The board finds that the claims according to the appellant's current main and auxiliary requests comply with the provisions of Article 123(2) and (3) EPC. Since this finding has not been in dispute during the present proceedings, there is no need for further detailed substantiation of this matter.

6. The respondent's submissions and the pieces of evidence submitted in the course of the opposition and subsequent appeal proceedings [see, in particular, the declarations by K. Wallevik (24), P. Kaersgaard (25) and J. Ingerslev (27), and the abstract of Dr Wallevik’s oral presentation allegedly presented to the public during or before the "symposium"] are, in the board's judgment, insufficient to prove in an unequivocal manner the respondent's allegation that (1) represents in every aspect a true and authentic account of the earlier oral presentation at the "symposium". Contrary to the opinion of the opposition division in the impugned decision, the board cannot come to an unequivocal conclusion on the arguments and evidence submitted on behalf of the parties removing the doubts raised by the appellant as to the relevance of citation (1) as part of the state of the art under Article 54(2) EPC.

The question of whether or not the content (1) forms part of the relevant state of the art needs not, however, be decided in the present case, because, on the one hand, the main and the first auxiliary must in any case fail for the reasons set out below on the basis of the state of the art considered in this decision and, on the other, the disclosure of (1) would not prevent the second auxiliary request being patentable, as it is the case with citation (26).

7. Consequently, when considering the state of the art as represented by citations 2 to 23 (see points 4.5 and 6 above), the board concurs with the respondent's view that the content of (2) comes closest to the claimed method for preparing a virus-inactivated protein-containing composition according to the main, first and

second auxiliary requests. This citation refers to a method for the inactivation of viruses in labile protein-containing blood products such as whole blood, blood plasma, blood plasma fractions and derivatives, eg factor I, factor III, factor V, factor VIII, factor XIII, the prothrombin complex (factors II, VII, IX, X), fibrinogen, HBsAg, alpha-, beta-, gamma-globulins, fibrinogen, fibronectin, antithrombin III, etc. (see eg claim 14). The particular method disclosed in (2) comprises the steps of contacting said blood products for a sufficient period of time with an effective amount of a di- or trialkyl phosphate as the organic solvent, preferably TNBP, in the presence or absence of a surfactant (wetting agent, detergent), followed by removing the di- or trialkyl phosphate, preferably together with the detergent employed during the S/D treatment (see especially column 9, lines 41 to 51).

7.1 While the TNBP treatment in the presence or absence of a detergent is described in (2) as being highly effective in the disruption of lipid-enveloped viruses and, consequently, in the inactivation of all kind of enveloped viruses, such as hepatitis B and non-B, non-A virus, cytomegalovirus, Epstein Barr viruses, herpes group viruses, lactic dehydrogenase viruses, etc., this treatment does not essentially affect non-enveloped viruses (see especially column 10, lines 33 to 41). Consequently, citation (2) already suggests to combine the S/D method disclosed in (2) with still other methods of inactivating viruses **including those for non-lipid coated viruses** and recommends for this employing a **heating step**, which can be effected in the presence of a protein stabilizer which stabilizes the labile protein against heat or a stabilizer which also tends to protect all protein, including components of

the virus against heat. Apart from the fact that (2) suggests to carry out the heating step for a sufficient period of time, e.g at least 5 hours and preferably at least 10 hours at a temperature of 50° to 70°C, especially 60°C (see especially column 9, line 59 to column 10, line 2), no specific or detailed mode of operation for the heating step is disclosed in (2).

7.2 In conclusion, while the disclosure of citation (2) is extremely precise and specific concerning the trialkyl phosphate treatment for the inactivation of enveloped viruses in labile, protein-containing compositions corresponding to steps (a) and (b) in present claim 1, it remains more or less general and unspecific, as far as the conditions for the heat treatment are concerned (see steps (c) and (d) in present claim 1).

*Main Request, First Auxiliary Request*

8. The first auxiliary request differs from the claims as granted (main request) solely by the additional specification in claim 1 requiring that the trialkyl phosphate treatment in step (a) be carried out in the presence of a surfactant which is subsequently removed in step (b) together with the trialkyl phosphate (see paragraph VII above). Since citation (2) already teaches TNBP treatment in the presence or absence of a surfactant (see point 7 above), the following observations and conclusions apply in every aspect equally to the main and first auxiliary request.

8.1 Thus starting from the above disclosure in (2) as representing the closest state of the art, the problem the claimed invention seeks to solve may be seen as that of reducing to practice and implementing the

above-mentioned teaching of citation (2). The solution to the problem proposed in claim 1 of the main and first auxiliary requests involves the combination of the trialkyl phosphate treatment as described in (2), optionally in the presence of a surfactant, with the steps of

(c) lyophilising and

(d) dry heat-treating the lyophilized, protein-containing composition to achieve effective inactivation of enveloped and non-enveloped viruses in said compositions.

8.2 On the basis of the state of the art available in the proceedings, the disclosure of the claimed invention in the patent in suit, in particular examples 1 to 5, and in the absence of any evidence to the contrary, the board is satisfied that the stated technical problem has been plausibly solved.

8.3 The board finds that none of citations 2 to 23 anticipates the proposed solution, that is to say the particular combination of chemical and physical treatment for the inactivation of viruses in protein-containing compositions including all the technical features stated in Claim 1 of the main or first auxiliary request. Since this has not been disputed, it is not necessary to give detailed reasons for the board's finding.

9. At the priority date of the patent in suit, it was part of the common general knowledge that the main heating methods used to inactivate viruses in a protein consisted in heat-treating the protein product in

solution, on the one hand, or heat-treating the dry protein product, on the other. Illustrative of this general knowledge is, for example, citation (11) which is an excerpt from a so-called **"Educational Book 1988"** of general interest and as such qualifies to illustrate common general knowledge.

9.1 Citation (11) refers in the context of the inactivation of viruses in protein products to the S/D method with TNBP, having the capability of destroying (disrupting) the lipid envelope of the virus and to heat treatment, having the capability of denaturating the viral protein and nucleic acid, as well. The two options for the heat treatment reported in (11) consist of either heating the protein product in solution, usually at 60°C for 10 hours, or dry-heating, such as conventional freeze drying of the protein product in its final container to a very low moisture content followed by heating under nitrogen or vacuum at 60° to 80° for 10-96 hours (see especially page 82, line 14 onwards). Moreover, the author of (11) already suggests in the penultimate paragraph on page 82 the possibility of using more than one inactivation principle when designing virus safety into protein products and refers in this respect to a thorough viricidal step during purification and a terminal dry-heating to counter possible recontamination.

The skilled person, knowing the prior art of (11) and faced with the question of whether the problem posed should preferably be solved by combining the known S/D treatment with either heating the protein in solution or dry heating would have learned from (11) that, although heating proteins in solution was possibly the most convincing way to destroy all blood borne viruses,

it causes severe denaturation of the desired protein unless a protective formulation is provided in the form of very high concentrations of inorganic salts, sugars or amino acids. This is, however, said in (11) to be associated with the disadvantages that the protective agents used protect also viruses from heat inactivation to some extent, are physiologically unacceptable and have thus to be removed by further processing.

Consequently, the teaching of (11) points the skilled person starting from (2) in the direction of choosing the combination of S/D treatment with dry heat treatment, preferably a terminal dry-heat treating step, to avoid the disadvantages associated with heating in solution and, moreover, to avoid recontamination.

9.2 The skilled man seeking further support for his choice in the state of the art, should he really need them, would have come upon document (6) which he would certainly have considered with great interest for the following reasons: the teaching of (6) corroborates that of (11), by stating that only a few plasma proteins, for instance albumin, can endure liquid-phase heat treatment without substantial denaturation and that plasma proteins having physiological or biological activity are particularly sensitive to heat and easily undergo thermal denaturation or degradation, which frequently results in reduction or total loss of their specific physiological or biological activity. He would, moreover, have learned from (6) that heat treatment of proteins in water-free or substantially water-free dry condition results in prevention, to a significant extent, of loss in activity as compared with the liquid phase heat-treatment. As can be derived

from table 1 in (6) (see end of page 7), heating coagulation factor VIII in solution, without addition of any stabilising agents, at 60°C for 20 hours results in a total loss of its activity, whereas dry-heat treatment of the dry lyophilised powder for the same period at the same temperature is capable of efficiently preserving factor VIII activity to an extent of 63.1% of that before heating.

The appellant has failed to persuade the board with his argument that the statement in the first full paragraph on page 2 of citation (6) had to be construed as representing a prejudice against using dry-heat treatment for the inactivation of non-lipid coated viruses. Apart from the fact that, according to the established jurisprudence (see Case Law of the Boards of Appeal of the EPO, 3rd edition 1998, D. 7.2) an alleged prejudice cannot be demonstrated by a statement in a single patent specification, the particular statement in (6) does not teach, contrary to the appellant's assertion, that dry-heating of proteins was incapable of destroying non-lipid coated viruses, but rather refers to the mechanism involved in the inactivation of lipid-coated viruses by dry-heat treatment.

That the alleged prejudice did not exist becomes moreover clear from a reference to the prior art of citations (8), (9A), (9B) and 11. Thus (8) teaches that virtually all kinds of viruses, that is to say non-enveloped and enveloped viruses, can be inactivated by heating proteins, for example enzymes, in the dry state (see especially the paragraph bridging pages 4 and 5). Exemplary non-enveloped viruses, which are destroyed by the method of dry-heating in (8) are

encephalomyocarditis (EMC), polio type 1, adeno type 5 and hepatitis A viruses (see especially Example 2, Example V). Both Citations (9A) and (9B) disclose that dry-heating was successfully used to inactivate the non-enveloped parovirus B19 in blood serum protein compositions. Finally, citation (11) refers to the inactivation of enveloped and non-enveloped viruses as well by dry heat-treatment involving the mechanism of denaturating the viral protein and nucleic acid (*loc. cit*.).

9.3 For all these reasons, the board concludes that the subject-matter of the main and first auxiliary requests results from an obvious combination of the teaching of citation (2) with that of (11) and is therefore devoid of inventive step contrary to the requirements of Article 52(1) in conjunction with Article 56 EPC.

*Second Auxiliary Request*

10. The second auxiliary request differs from the claims as granted (main request) by the additional specification in claim 1 requiring that the trialkyl phosphate treatment in step (a) be carried out in the presence of a protease inhibitor which is subsequently removed in step (b) together with the trialkyl phosphate (see paragraph VII above).

10.1 As has credibly been demonstrated by the tests carried out in the patent in suit, the S/D treatment of proteins, as described in citation (2), is frequently associated with a substantial reduction of the desired physiological activity and degradation of the protein treated. Thus, in the case of thrombin, the treatment with 0.3% (w/v) TNBP and 1% (w/v) Tween 80 as the

detergent (surfactant) at 30°C reportedly resulted in a significant loss of its activity after 30 hours, and it was judged that 90% activity was difficult to be maintained even after 6 hours of treatment (see Experiment Example 2, Figures 3 and 4). The same treatment of fibrinogen reportedly resulted in a total loss of activity after 24 hours (see Experiment Example 2, Figure 5). When fibronectin was subjected to the above-mentioned treatment, after 6 hours a residual gelatin binding activity ratio of 85% was found which deceased to 55% after 30 hours of treatment (see Experiment Example 3, Tables 5 and 6).

Thus, starting from the above disclosure in (2) as representing the closest state of the art, the technical problem, which the invention set out in claim 1 of the second auxiliary request seeks to solve, consists, **in addition** to the problem underlying the main and first auxiliary requests, in improving the trialkyl phosphate (TNBP/D) treatment in step (a) of the claimed process in terms of reducing the protein's loss of activity and preventing its degradation during said treatment. According to claim 1 it is suggested to carry out the trialkyl phosphate treatment in step (a) in the presence of a protease inhibitor in order solve this additional problem.

10.2 The experimental data in the contested specification show that thrombin activity reduction was successfully suppressed by the addition of EACA (å-aminocaproic acid) or arginine as the protease inhibitors. For example, When EACA was added in the concentration above 2%, more than 90% activity was reportedly maintained after 30 hours treatment with 0.3% (w/v) TNBP and 1% (w/v) Tween 80 at 30°C (cf. Figs. 3 and 4). In the case

of fibrinogen, both aprotinin and EACA were shown to have a stabilising effect, with EACA at a concentration above 5% being capable of maintaining 90% activity after 30 hours treatment under the conditions mentioned above (see Figure 5). Similarly, the data in the contested patent show that addition of EACA at a concentration above 2% or aprotinin at a concentration of 10 units/ml resulted in a significant suppression of loss or reduction of fibrinogen activity.

These results suggest that the additional problem defined above is adequately solved.

10.3 In his written submissions and during the oral proceedings, the respondent suggested that the limited experimental data provided in the contested patent specification were insufficient to clear any remaining doubts as to whether the presence of a protease inhibitor during the trialkyl phosphate treatment in step (a) would generally be necessary and useful and would, moreover, indeed be effective in preventing loss of activity and degradation in all kinds of proteins, but did not substantiate this by any evidence. However, a mere doubt on the part of the respondent cannot prevent the beneficial effects and capabilities, ascribed in the patent in suit to the use of a protease inhibitor, being taken into account when formulating the problem and assessing its solution. The board is satisfied that the subject-matter of claim 1 of the second auxiliary request plausibly solves the technical problem in its entirety, including the additional technical problem defined above.

11. The question of novelty of the second auxiliary request was not at issue during the appeal proceedings and the

board sees no reason to raise this question on its own motion. The method of claim 1 and dependent claims 2 to 7, therefore, is novel.

12. The only issue remaining is therefore whether the proposed solution involves an inventive step.

12.1 Although the inventors of (2) describe in the their patent specification with the utmost care all conceivable aspects of the TNBP/D treatment of proteins, they are entirely silent about the possibility of carrying out this treatment in the presence of any kind of protein stabilizer, let alone a protease inhibitor. The idea that they had simply forgotten or did not think of this possibility must reasonably be excluded, since citation (2) explicitly suggests in the context of the subsequent heat treatment, although optional in (2), the use of a protein stabilizer and refers in this respect to an agent which stabilizes the labile protein (see especially column 9, lines 61 to 66).

The same considerations apply to the disclosure of citation (11). Whereas (11) describes the beneficial effect of using "protective formulations" of different kinds to avoid denaturation of the desired protein during heat treatment, it is likewise entirely silent about the possibility of using a "protective formulation", let alone a protease inhibitor, during the TNBP/D treatment. Consequently it is virtually impossible that a person skilled in the art could derive from the most relevant disclosure in the state of the art any hint whatsoever leading him to the idea of carrying out the TNBP/D treatment in the presence of a protease inhibitor.

12.2 Citation (10) refers to the problem of reducing loss of Factor VIII procoagulant activity (Factor VIII:C) following blood collection and is thus far away from being concerned with the problem of inactivating viruses in protein products. It appears worthwhile to note, that (10) teaches, *inter alia*, that the addition of various protease inhibitors such as benzamidine, phenylmethylsulfonyl fluoride (PMSF), aprotinin, or soybean trypsin inhibitor (SBTI) **failed to provide significant protection** against decay of Factor VIII:C activity. In this case, neither the rate of decay in the first 24 hours nor the Factor VIII:C activity after storage for 48-72 hours were significantly altered (see especially page 521, Abstract: lines 1 to 10; page 525, last paragraph). Heparin and DFP are reported to give complete protection only for a few hours, while by 24 hours the DFP-treated CPD plasma retained only 78% of the initial plasma activity and 51% remained with the heparin treatment (see especially page 525, last paragraph).

Apart from the fact that the results reported in (10) are far from being promising or encouraging, the skilled person had no sound reason to combine the teaching of citation (10) concerned with the problem of reducing the loss of Factor VIII:C activity following blood collection with the claimed subject-matter in the patent in suit relating to a highly specific and elaborated method of inactivating viruses. It was, moreover, well known to a person skilled in the art that the action of an enzyme, such as a protease, on a substrate is an extremely specific one and depends considerably on the particular milieu in which, and the particular conditions, under which the enzyme is used. Accordingly, citation (10) could not provide any basis

for prediction with any certainty that proteases would indeed act as effective stabiliser during virus-inactivation of proteins with trialkyl phosphate.

12.3 The respondent has provided with the reply to the statement of the grounds of appeal a series of additional documents relating to the use protease inhibitors for various applications (see point 4.3 above). The board having considered these documents has come to the conclusion that none of them contains a teaching which would be more relevant to the assessment of inventive step than what has already been under consideration in foregoing points 11.1 and 11.2, since none of them refers to the use of protease inhibitors in a method for the inactivation of viruses either.

12.4 Therefore, in the Board's judgement, the subject-matter of claim 1 in accordance with the second auxiliary request involves an inventive step. Dependent Claims 2 to 7, which relate to preferred embodiments of claim 1, derive their patentability from Claim 1.

## Order

## For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent with the following claims and a description to be adapted:

Claims 1 to 7, filed as the second auxiliary request on 23 January 2001 with the appellant's letter dated

22 January 2001.

The Registrar: The Chairman:

A. Townend P. A. M. Lançon