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Datasheet for the decision of 30 July 2020

Case Number: T 0115/18 - 3.3.04

Application Number: 00992709.6

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Language of the proceedings: EN

Title of invention:
Method of preparing alpha-1 proteinase inhibitor

Patent Proprietor:
Grifols Therapeutics Inc.

Opponents:
Baxalta GmbH
Kamada Ltd.

Headword:
Alpha-1 proteinase inhibitor/GRIFOLS

Relevant legal provisions:
EPC Art. 123(3), 56

Keyword:
Main request - inventive step (no)
Auxiliary request 1 - inventive step (yes), extension of scope of protection (no)

Decisions cited:
T 0939/92

Catchword:

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Beschwerdekammern

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Case Number: T 0115/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 30 July 2020

Appellant: (Opponent 1)	Baxalta GmbH Thurgauerstrasse 130 8152 Glattpark (Opfikon) (CH)
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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 November 2017 concerning maintenance of the European Patent No. 1343809 in amended form.**

Composition of the Board:

Chairman	P. de Heij
Members:	D. Luis Alves
	B. Claes

Summary of Facts and Submissions

I. The appeal was filed by opponent 1 (appellant) against the interlocutory decision of the opposition division that, account being taken of the amendments in the form of auxiliary request 2, the patent in suit and the invention to which it related met the requirements of the EPC (Article 101(3)(a) EPC).

Claim 1 of this request read:

"1. A method for purifying α-1 proteinase inhibitor from an aqueous solution containing α-1 proteinase inhibitor, comprising the steps of:

a) removing a portion of contaminating proteins from the aqueous solution to obtain a purified solution containing α-1 proteinase inhibitor, wherein said removing step comprises the steps of

(i) precipitating said portion of contaminating proteins from said aqueous solution by adding a polyethylene glycol with a MW between about 3,000 and about 4000 to said aqueous solution at a concentration between about 3% to 15% weight per volume, and adjusting the pH of said aqueous solution from about 5.0 to about 6.0; and
(ii) separating said precipitated portion of contaminating proteins from said aqueous solution, thereby obtaining said purified solution containing α-1 proteinase inhibitor; then

(b) inactivating viruses prior to diluting said purified solution to reduce the conductivity of said purified solution so that α-1 proteinase inhibitor binds to an anion exchange resin, wherein said virus inactivation step comprises the steps of

(a) adding a detergent to said purified solution to obtain a mixture of detergent and purified solution; and

(b) adjusting the pH of said mixture to from about 6.5 to about 8.5, and wherein said detergent is a non-ionic detergent; then

(c) passing said purified solution through the anion exchange resin so that α-1 proteinase inhibitor binds to said anion exchange resin; then

(d) eluting α-1 proteinase inhibitor from said anion exchange resin to obtain an eluted solution containing α-1 proteinase inhibitor; then

(e) adjusting the pH, conductivity and protein concentration of said eluted solution containing α-1 proteinase inhibitor so that α-1 proteinase inhibitor does not bind to a cation exchange resin;

(f) passing the eluted solution through a cation exchange resin; and

(g) collecting a flow-through from said cation exchange resin that contains α-1 proteinase inhibitor."

Independent claim 2 differed from claim 1 in that reference was made to "Cohn fraction IV-1" instead of "aqueous solution" and in step (b) reference was made to adjusting the conductivity of the purified solution instead of diluting the purified solution.

II. The patent, entitled "*Method of preparing alpha-1 proteinase inhibitor*", was granted on European patent application No. 00 992 709.6, which was filed as an international application published as WO 02/48176.

Claim 1 as granted read:

"1. A method for purifying α-1 proteinase inhibitor from an aqueous solution containing α-1 proteinase inhibitor, comprising the steps of:

a) removing a portion of contaminating proteins from the aqueous solution to obtain a purified solution containing α-1 proteinase inhibitor, wherein said removing step comprises the steps of

(i) precipitating said portion of contaminating proteins from said aqueous solution by adding a polyethylene glycol with a MW between about 3,000 and about 4000 to said aqueous solution at a concentration between about 3% to 15% weight per volume, and adjusting the pH of said aqueous solution from about 5.0 to about 6.0; and
(ii) separating said precipitated portion of contaminating proteins from said aqueous solution, thereby obtaining said purified solution containing α-1 proteinase inhibitor; then

(b) diluting said purified solution to reduce the conductivity of said purified solution so that α-1 proteinase inhibitor binds to an anion exchange resin; then

(c) passing said purified solution through the anion exchange resin so that α-1 proteinase inhibitor binds to said anion exchange resin; then

(d) eluting α-1 proteinase inhibitor from said anion exchange resin to obtain an eluted solution containing α-1 proteinase inhibitor; then

(e) adjusting the pH, conductivity and protein concentration of said eluted solution containing α-1 proteinase inhibitor so that α-1 proteinase inhibitor does not bind to a cation exchange resin;

(f) passing the eluted solution through a cation exchange resin; and

(g) collecting a flow-through from said cation exchange resin that contains α-1 proteinase inhibitor."

Claim 2 as granted read:

"2. A method for purifying α-1 proteinase inhibitor from Cohn Fraction IV-1, comprising the steps of:

a) removing a portion of contaminating proteins from the Cohn Fraction IV-1 in order to obtain a purified solution containing α-1 proteinase inhibitor, wherein said removing step comprises the steps of

(i) precipitating said portion of contaminating proteins from said Cohn Fraction IV-1 by adding a polyethylene glycol with a MW between about 3,000 and about 4000 to said Cohn Fraction IV-1 at a concentration between about 3% to 15% weight per volume, and adjusting the pH of said aqueous solution from about 5.0 to about 6.0; and

(ii) separating said precipitated portion of contaminating proteins from said Cohn Fraction IV-1, thereby obtaining said purified solution containing α-1 proteinase inhibitor; then

(b) adjusting the conductivity of said purified solution so that α-1 proteinase inhibitor binds to an anion exchange resin; then

(c) passing said purified solution through the anion exchange resin so that α-1 proteinase inhibitor binds to said anion exchange resin; and then

(d) eluting α-1 proteinase inhibitor from said anion exchange resin to obtain an eluted solution containing α-1 proteinase inhibitor; then

(e) adjusting the pH, conductivity and protein concentration of said eluted solution containing α-1 proteinase inhibitor so that α-1 proteinase inhibitor does not bind to a cation exchange resin;

(f) passing the eluted solution through a cation exchange resin; and

(g) collecting a flow-through from said cation exchange resin that contains α-1 proteinase inhibitor."

III. Two oppositions had been filed. The patent had been opposed as a whole under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), as well as under Article 100(b) and Article 100(c) EPC.

IV. In their statement setting out the grounds of appeal, the appellant contested the reasoning of the opposition

division with regard to inventive step (Article 56 EPC). Further, they submitted that, depending on how the claims were construed, the requirements of Article 123(3) EPC were not met.

V. With their reply to the statement of grounds of appeal, the patent proprietor (respondent) filed auxiliary claim requests 1 to 7. The main claim request corresponds to the request found allowable by the opposition division.

Claims 1 and 2 of **auxiliary request 1** differ from claims 1 and 2 of the main request, respectively, by the following additional feature in step (b)(b):

"and wherein said non-ionic detergent is Tween 20".

VI. The board summoned the parties to oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA.

VII. Further submissions were filed by the respondent and appellant by letters dated 18 and 22 June 2020 respectively.

VIII. By letter dated 22 June 2020, the respondent requested that the oral proceedings be postponed.

IX. In its communications dated 29 June 2020 and 15 July 2020, the board addressed the respondent's request for postponement and informed the parties that the date for oral proceedings was maintained.

X. Opponent 2 filed no substantive submissions in the appeal proceedings.

XI. Opponent 2 was not represented at the oral proceedings, as they had indicated in a letter dated 29 July 2020. At the end of the oral proceedings the chair announced the board's decision.

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

D4: US 4,379,087

D5: US 5,610,285

D8: US 5,616,693

D9: Coan, M.H. *et al*, Vox Sang. 46, 1985, pages 333-342.

D10: Coan, M.H., The American Journal of Medicine, 84 (suppl. 6A), 1988, pages 32-36.

D11: Hein *et al*, Eur. Respir. J. 3 (suppl. 9), 1990, pages 16S-20S.

D24: US 4,540,573

D35: "Test report 2 and experimental data".

D37: Package insert of Prolastin, Rev. January 2005.

D38: Gadek, J.E., Am. J. of Medicine 84 (suppl. 6A), 1988, pages 1-2.

D39: Clark J.A. *et al*, Am. J. of Medicine 92, pages 621-626.

D40: Dt. Ärztebl. 86 (Heft 19), 1989, pages A1441-A1442.

D41: Physician's Desk Reference, Prolastin, 1994, pages 1611-1612.

XIII. The appellant's arguments, insofar as relevant to this decision, may be summarised as follows:

Main request - claim 1

Inventive step - Article 56 EPC
Document D4 as closest prior art

The claimed invention differed from the method described in document D4 only by the steps of detergent virus inactivation and of cation exchange chromatography.

These differences did not serve the same purpose. They thus related to two different and independent technical problems which should be addressed separately.

The first difference did not result in improved virus clearance. Nor did it result in a shorter production time: the patent indicated a detergent virus inactivation step of 8 to 10 hours (see column 10, line 1), which compared with a heat inactivation step lasting up to 10 hours in document D4 (column 4, line 45).

The first objective technical problem could thus be formulated as the provision of an alternative method for purifying α-1 proteinase inhibitor (α1-PI).

The claimed solution was obvious because it was known to the skilled person from document D8 that detergent inactivation reduced the virus content (column 4, lines 15 and 34).

No improvement could be ascertained from the disclosure in the patent or from the disclosure in the post-filed evidence document D35 for the second difference either. This document compared a method according to document D11, represented by example 1, with two methods according to the patent, illustrated by examples 2 and 3. Firstly, the methods in examples 2 and 3 were not improved over the method in example 1. Secondly, the method in example 1 did not correspond to the method disclosed in document D4, and the experiments differed from each other and from the claimed method in several features, thus not allowing any effect to be attributed to any specific one of those differences. Specifically, at least the following differed between examples 2 and 3 on the one hand and example 1 on the other hand: input α1-PI solution, chromatography column and extra intermediate steps. Further, the examples in document D35 used additional method steps which were not even required by claim 1, such as diafiltration and nanofiltration steps.

In the absence of an identified technical effect, the objective technical problem addressed by the step of cation exchange chromatography was to be formulated as the provision of an alternative method for purifying α1-PI.

The claimed solution was obvious to the skilled person from the disclosure in document D5, column 6, lines 49 to 56.

Should the objective technical problem be formulated as taking into account an improvement in purity due to the cation exchange chromatography step, then the solution would nevertheless be obvious from document D5, which disclosed an additional cation exchange chromatography step which could be applied to any starting material (column 3, line 35).

Amendments - Extension of protection conferred by the patent - Article 123(3) EPC

The wording of the claim did not rule out the claimed methods including additional steps between the precipitation of α1-PI in step (a) and the dilution in step (b), in particular not the forming of an intermediate paste. The wording "diluting said purified solution" in step (b) did not mean exactly the same solution as that in step (a).

If the wording "said solution" meant "the same solution", then claims 1 and 2 as granted would exclude any method step between the PEG precipitation and the anion exchange chromatography. In that case, the introduction of a virus inactivation step between those steps, as in claim 1 of the main request, would constitute an extension of the scope of protection.

Auxiliary request 1 - claims 1 and 2

Inventive step - Article 56 EPC
Document D4 as closest prior art

Document D8 disclosed a method of purifying α1-PI involving a virus inactivation step with Tween 80, instead of Tween 20 as specified in auxiliary

request 1. In the absence of any technical effect associated with this difference, the objective technical problem was the provision of an alternative virus-inactivating substance.

The solution to this problem was the selection of an equivalent detergent. Document D24 disclosed Tween 20 (paragraph bridging columns 7 and 8). Tween 20 constituted an arbitrary choice from detergents used in protein production processes. Moreover, the disclosure in document D8 did not relate solely to Tween 80. The document disclosed the use of detergent treatment in general (column 4, lines 7 to 31, in particular lines 17 and 27).

Therefore the claimed subject-matter did not involve an inventive step.

Document D5 as closest prior art

Document D5 (see example 3) disclosed a method for purification of α1-PI starting from Prolastin. The method steps for preparing Prolastin were thus implicitly disclosed and were known from each of documents D4, D9, D10 and D11, and included steps (a), (c) and (d) of the claimed method, as well as the part of step (b) consisting of dilution.

For a disclosure to be implicit it needs to be immediately apparent to the skilled person. Prolastin was commonly prepared by the method developed by Dr. Coan and colleagues for the company Cutter Biological of Miles. Documents D37 to D41 represented this common general knowledge. Moreover, documents D37 and D41 referred to document D9, and documents D37 and D39 referred to document D10.

To the skilled person it was immediately apparent that the Prolastin used in example 3 was prepared according to the method used for the production of this commercially-available product. Thus the method steps were implicitly disclosed in example 3 of document D5.

It was not necessary for document D5 to contain a reference to documents D9 or D10. The absence of a reference to a particular document did not mean that its content was not included in the state of the art. This could be part of the "mental furniture" of the skilled person (see decision T 939/92).

XIV. The respondent's arguments, insofar as relevant to this decision, may be summarised as follows:

Request for postponement of the oral proceedings

The request was based on the following reasons: "*The proprietor and its representatives expect to be affected by travel restrictions, preventing attendance at the oral proceedings scheduled for July 30, 2020*".

Main request - claim 1

Inventive step
Choice of closest prior art

The patent aimed at improving the best method for purifying α1-PI commonly known in the technical field at the time of the invention. Since the commercial purification method disclosed in document D11 constituted an improvement of the method disclosed in document D4, the skilled person would not consider the method disclosed in document D4.

Document D4 as closest prior art

The claimed method was distinguished from the method disclosed in document D4 by the steps of detergent virus inactivation and cation exchange chromatography.

There was no functional link between the distinguishing features, which addressed different purposes. There was however a functional link between the first distinguishing feature, the detergent virus inactivation step, and the absence of a second PEG precipitation step in the method.

The technical effect of the detergent virus inactivation was a shorter production time. The step of heat inactivation used in the method disclosed in document D4 lasted approximately 10 hours (column 5, line 45). In contrast, post-published document D35 reported on experiments according to the claimed method involving a step of detergent inactivation lasting 5 hours.

The first objective technical problem was thus the provision of a method for purifying α1-PI within a shorter production time.

The solution was not obvious from document D4 itself, which did not disclose virus inactivation steps other than heat treatment.

Nor was the solution obvious from document D8, because the skilled person would not isolate a single step of a method and apply it to another method. Furthermore, since the disclosed method involved a step of precipitation of α1-PI by $ZnCl_2$, if the skilled person

were to apply the detergent inactivation step used in this method they would include the $ZnCl_2$ precipitation step as well.

The technical effect of the cation exchange chromatography steps was increased yield and purity. This was shown in document D35, which provided a comparison with the method disclosed in document D11. Since the method disclosed in document D11 constituted an improvement over the method disclosed in document D4, an increase in purity and yield associated with the former method also applied to the latter one.

To increase both yield and purity was a challenge for the skilled person as the two were inversely related. Document D4 did not provide the skilled person with any motivation to modify the method by introducing a cation exchange chromatography step. The skilled person would have expected any additional step to lead to an increase in purity and concomitant decrease in yield.

The patent disclosed that the method disclosed in document D5 was not suitable in practice because it involved too many resources. Thus the skilled person seeking to solve the objective technical problem would not combine steps of that method with those of the method disclosed in document D4.

If the objective technical problem were to be formulated taking into account only the increase in purity, then the solution would likewise not be obvious. The skilled person would have expected an increase in purity to be accompanied by a decrease in yield. The skilled person would furthermore not necessarily expect increased purity from the Prolastin method of document D5. The skilled person had no reason

to expect increased purity and yield compared to the commercially-available method.

Amendments - extension of protection conferred by the patent - Article 123(3) EPC

The claim wording excluded the formation of a paste between the steps of PEG precipitation and anion exchange chromatography. However, claim 1 as granted did not exclude every intermediate method step. Thus the amendment of introducing a step of virus inactivation did not result in an extension of the protection conferred by the patent.

Auxiliary request 1

Inventive step - Article 56 EPC
Document D4 as closest prior art

Even if the skilled person were to modify the method disclosed in document D4 by carrying out a detergent virus inactivation as disclosed in document D8, they were directed to no other detergent than Tween 80. The skilled person had no reason to deviate from the teaching in this document. Moreover, the skilled person would not be motivated to do so because they did not know whether a different detergent would work.

The disclosure of Tween 20 in document D24 concerned its use as a wetting agent, not for virus inactivation. In that document, the virus-inactivating agent was a di- or trialkylphosphate. There was no evidence on file that it was common general knowledge that other detergents were interchangeable with Tween 80 for the purpose of virus inactivation.

Document D5 as closest prior art

Example 3 of document D5 disclosed steps corresponding to steps (e), (f) and (g) of the claims at issue. However, the remaining steps were not disclosed. The overall method as claimed was not disclosed because in example 3 the skilled person starts from a commercially-available product.

The common general knowledge of the skilled person was not what they could easily find out. Moreover, it had not been shown that the skilled person would know that the product sold under the trademark Prolastin was produced according to document D9.

XV. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the appeal be dismissed (i.e. that the patent be maintained on the basis of the set of claims as upheld by the opposition division, here main request), or, alternatively, that the patent be maintained on the basis of the claims according to auxiliary request 1, filed with the reply to the statement of grounds of appeal.

Reasons for the Decision

Admissibility of the appeal

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

Request for postponement of the oral proceedings

2. The respondent requested postponement of the oral proceedings. The reasons indicated were a very general reference to the ongoing COVID-19 pandemic and expected travel restrictions.

3. However, the board was not presented with information on travel restrictions between The Netherlands, where the representative for the respondent was located, and Munich or Munich and The Netherlands in force at the time the request was filed or up to the date of the oral proceedings. Therefore the request was not allowed and the oral proceedings were not postponed.

Party not represented at oral proceedings

4. As announced by letter of 29 July 2020, opponent 2, a party as of right, did not attend the oral proceedings (see section XI.). In accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the oral proceedings were held without it. By its decision not to attend the oral proceedings, this party chose not to make any submissions during such proceedings.

Main request - claim 1

5. Inventive step - Article 56 EPC

Closest prior art

5.1 There was disagreement between the parties as to which disclosure represented the closest prior art to the subject-matter of claim 1. The appellant submitted

lines of argument starting from each of documents D4 and D5; the respondent considered the disclosure of document D11 to constitute the closest prior art.

5.2 Document D4 discloses a method of purifying α-1 proteinase inhibitor (α1-PI) comprising steps of PEG precipitation, dilution and anion exchange chromatography. It thus addresses the same purpose as, and discloses a method having several steps in common with, the claimed method. The board holds this to be a suitable starting point for the assessment of inventive step.

The respondent argued that document D11 represented an even closer disclosure to the claimed subject-matter. However, whether other documents constitute a more promising starting point for the assessment of inventive step than a given document is considered immaterial in the present case, since the board holds that the claimed invention is obvious when starting from the disclosure in document D4.

Objective technical problem - partial problems

5.3 It was common ground that document D4 disclosed a method of purifying α1-PI comprising steps (a), (c), (d) and part of step (b) (the dilution) as defined in the claim.

The claimed method differs therefrom by the additional method steps of the virus inactivation part of step (b) and steps (e) to (g) defining a cation exchange chromatography step.

5.4 As regards the technical effect associated with these distinguishing features, it was reasoned by the

appellant that each feature should be analysed in isolation since they were not technically interrelated. The respondent conceded that there was no technical interrelation between the virus inactivation and the cation exchange chromatography. A technical interrelation between the virus inactivation and the cation exchange chromatography is not apparent to the board either. In view of the above, the board will address the technical effect resulting from each feature in turn.

The respondent submitted that the first distinguishing feature - the detergent virus inactivation step - and the absence of a second PEG precipitation step (i.e. precipitation of α1-PI) in the method were technically interrelated. The board notes, however, that the absence of a second PEG precipitation step is not a feature which distinguishes claim 1 from the method disclosed in document D4. Thus such a technical interrelation is immaterial for the present analysis, which relies on the technical effects that can be attributed to the features distinguishing the claimed subject-matter from the closest prior art.

First partial technical problem and obviousness - virus inactivation step

Objective technical problem

5.5 With regard to the step of virus inactivation by detergent, no technical effect has been demonstrated beyond that already achieved by the method disclosed in document D4. The board therefore formulates the partial objective technical problem as the provision of an

alternative method for purifying α1-PI including virus reduction.

5.6 The respondent reasoned that the experimental report document D35 showed a method of purifying α1-PI according to the patent which involved a step of detergent virus inactivation taking 5 hours. Thus the objective technical problem solved was the provision of a method for purifying α1-PI with a shorter production time.

5.7 The board notes, however, that according to the patent the solvent-detergent virus inactivation step takes between 8 and 10 hours (column 10, line 1). On the other hand, document D4 discloses that the heat inactivation step takes up to 10 hours (column 5, line 45). Although document D35 shows an example involving a shorter step of virus inactivation, the claimed method is not restricted to said example.

Thus the duration of the solvent-detergent virus inactivation as disclosed in the patent is not shorter than that of the heat inactivation used in the prior art method under discussion. Therefore the board cannot accept the respondent's reasoning.

Obviousness

5.8 It is established case law of the boards of appeal of the EPO that, when the objective technical problem addressed is the provision of an alternative, as in the case at hand, an arbitrary selection from amongst a number of known possible solutions cannot be considered to involve an inventive step (see for example decision T 939/92, reasons 2.5.3).

5.9 The skilled person would have been aware of the contents of document D8, which is directed to the purification of the same product by means of a method involving PEG precipitation and anion exchange chromatography. This document aims at improving prior methods comprising various combinations of one or more PEG precipitation steps, one or more chromatographic steps and phase separations (column 2, lines 25 to 27). It discloses a method involving a first precipitation step using PEG, which results in precipitation of contaminating proteins, and a second precipitation step using $ZnCl_2$, which results in precipitation of α1-PI. These steps are followed by re-solubilisation of α1-PI and by virus inactivation. This latter step involves the addition of a solvent-detergent containing Tween 80 in TNBP. The resulting solution is used directly in the anion exchange chromatography step (column 2, lines 40 to 65).

5.10 Document D8 thus taught the skilled person that, in a multi-step process for α1-PI purification, one possibility of carrying out virus inactivation was by using the detergent Tween 80.

5.11 The skilled person seeking to provide an alternative method for purifying α1-PI including virus reduction would thus introduce the virus inactivation step by detergent Tween 80 before dilution of the solution for anion exchange chromatography, as disclosed in document D8, in the method as disclosed in document D4. It follows that the skilled person would arrive at the claimed subject-matter in an obvious way.

5.12 The respondent submitted that the skilled person would not arrive at the claimed method in an obvious way, based on the following, similar, arguments: document D4

provided no indication of the solution because it mentioned only heat inactivation; the skilled person would not isolate one method step from the method disclosed in document D8 and apply it to a different method; the skilled person would not combine the two teachings because the method disclosed in document D8 involves precipitation of the product, which is excluded by the claimed method; the skilled person would have been dissuaded from isolating the virus inactivation step from the $ZnCl_2$ precipitation step and would thus at best have applied both steps as disclosed in document D8 to the method disclosed in document D4.

5.13 To the person skilled in the field of downstream processing of biological molecules, various unit operations are tools of which use can be made depending on the objective in terms of yield and purity. Beyond that, the choice of unit operations as well as their sequence is limited only insofar as each input stream needs to be compatible with the corresponding unit operation. Thus to the skilled person the unit operations virus inactivation, precipitation, filtration and ion exchange chromatography are not undissociable as submitted by the respondent. Therefore the board takes the view that the skilled person would recognise that the solvent-detergent virus inactivation used in the method disclosed in document D8 was a possible solution for carrying out virus inactivation in other purification methods, and in particular in the method disclosed in document D4, all the more so since in the method disclosed in document D8 the virus inactivation step is directly followed by the anion exchange chromatography without any technical difficulties being reported. This is precisely the sequence of steps in the method as claimed. In light of the above and in the absence of reasons specific to the

unit operations of viral inactivation and anion exchange chromatography, the respondent's argument that the skilled person would not take a single step from one method and include it in a different method or use it in a different order of steps is not held to be convincing.

Second partial technical problem and obviousness - cation exchange chromatography steps

Objective technical problem

5.14 The respondent relied on document D35 to demonstrate that the effect of the cation exchange chromatography steps is to increase both purity and yield of the product.

This document is an experimental report submitted by the respondent, providing results in relation to the product purity and yield of two methods of α1-PI purification: a first method according to experiment 1, which represents the method disclosed in document D11, and a second method according to experiments 2 and 3, which falls within the scope of claim 1.

The board observes that the protocols used in experiment 1 on the one hand and experiments 2 and 3 on the other hand differ in a number of parameters, including the input solution into the PEG precipitation, the number of PEG precipitation operations, the anion exchange column used and corresponding buffer elution conditions, and the number of filtration operations. Indeed, whereas all the experiments have Cohn fraction IV-1 paste as input, the preparation of the starting aqueous solution differs between the experiments. The same applies to the column

used for anion exchange chromatography - in the case of experiment 1 a weak anion exchange column and in the case of experiment 2 a strong one - the elution conditions hence differing between the experiments. However, the column and the elution conditions affect the purity and yield of the product. The board further notes that in experiments 2 and 3, which represent the claimed method, there are a number of filtration steps not present in experiment 1, which represents the method of document D11, such as a diafiltration step after the anion exchange chromatography and additional nanofiltration and ultrafiltration steps after the cation exchange chromatography. Such steps have an impact on the purity of the final product and the yield of the method.

5.15 To be able to draw conclusions about the technical effect of a given feature, the experiments submitted must be designed such that the results are truly comparable. In the present case, experiments 2 and 3 should differ from experiment 1 only by the steps of cation exchange chromatography. However, as listed above, the experiments differ in method steps which are not technically related to this step, namely the starting aqueous solution, and the anion exchange chromatography and filtration steps downstream from the cation exchange chromatography. These differences have an impact on the yield and purity of the product. Therefore the board cannot conclude from the content of document D35 that the cation exchange chromatography steps lead to an increase in both purity and yield of the product.

5.16 In an auxiliary line of argument, the respondent submitted that the objective technical problem solved

by the claimed method was the provision of a method of purifying α1-PI with improved purity.

Obviousness

5.17 Document D5, which deals with the purification of the very same product, discloses the use of cation exchange chromatography as a technical development. Cation exchange chromatography is disclosed for use with a number of starting materials (including Cohn fraction IV-1 paste and purified α1-PI) and in combination with a number of other unit operations (column 3, lines 35 to 58). In example 1, cation exchange chromatography is used in combination with a number of other unit operations, following anion exchange chromatography; in example 3 it is applied directly to Prolastin, a commercially-available product containing α1-PI. This document reports that 90% yield and 95% purity can be achieved after two cation exchange chromatography steps (column 2, lines 27 to 36).

In view of the expected improvements in purity as reported in document D5, the skilled person, starting from the method of purifying α1-PI disclosed in document D4 and seeking to improve the purity achieved, would thus have used cation exchange chromatography as an additional method step. Thus the claimed method was obvious to the skilled person.

5.18 In view of the conclusions reached in points 5.11, 5.13 and 5.17, each of the features distinguishing the claimed method from the method of purifying α1-PI disclosed in document D4 is obvious to the skilled person. The claimed subject-matter therefore lacks inventive step as required by Article 56 EPC.

Auxiliary request 1 - claims 1 and 2

6. Inventive step - Article 56 EPC

6.1 The claimed methods differ from those of claims 1 and 2 of the main request, respectively, in that the non-ionic detergent in auxiliary request 1 is specified to be Tween 20 (see section V.).

Closest prior art

6.2 The appellant reasoned that the claimed methods did not involve an inventive step when starting from either one of document D4 and document D5 as representing the closest prior art to the claimed subject-matter.

Closest prior art document D4

6.3 Compared with the technical effects as discussed with regard to the main request (see points 5.4, 5.5, 5.15 and 5.16), no additional technical effects due to the use of Tween 20 have been put forward by the respondent.

Thus the partial objective technical problem that can be derived from the detergent virus inactivation step remains the provision of an alternative method for purifying α1-PI including virus reduction.

6.4 Document D8 discloses (see points 5.9 and 5.10) a method involving detergent virus inactivation using a non-ionic detergent - Tween 80 - without mentioning other detergents, such as Tween 20. The question to be addressed is thus whether the skilled person seeking to solve the technical problem would have modified the method disclosed in document D4 by introducing a step

of detergent virus inactivation prior to the anion exchange chromatography and would have modified that step so as to use a different detergent.

In the board's view, in the absence of any identified pointer to Tween 20, the claimed solution was not obvious to the skilled person unless, as was argued by the appellant with reference to document D24, Tween 80 and Tween 20 were known to the skilled person as being equally suitable for virus inactivation in protein production processes.

The passage from document D24 cited by the appellant (paragraph bridging columns 7 and 8) reads: "*Preferred wetting agents are non-toxic detergents. [...] In particular there is contemplated detergents which include polyoxyethylene derivatives of fatty acids, partial esters of sorbitol anhydrides, for example, those products known commercially as "Tween 80", "Tween 20" and "polysorbate 80" and nonionic oil soluble water detergents such as that sold commercially under the trademark "Triton X 100"* [...]". The board therefore notes that the references in this passage to the use of Tween 20 do not concern a virus inactivation activity but rather its use as a wetting agent. Document D24 is therefore silent on the appellant's allegation that the detergents are equivalent for the purpose they serve in the method claimed, i.e. virus inactivation.

6.5 The appellant further submitted that in addition to the use of the specific compound Tween 80 in column 4, lines 17 and 27, document D8 also generically discloses the use of "solvent-detergent treatment" in virus inactivation (column 4, lines 15 to 16).

The passage referred to reads: "*The alpha-1-PI-containing solution is virus inactivated by solvent-detergent treatment. A solution of 10±1% wt/v polysorbitol 80 and 3±0.31% wt/wt tri-n-butyl phosphate is added to the alpha-1-PI solution to a final concentration of [...]*". In the board's reading this passage leaves no room for an alternative detergent to be selected. The board therefore cannot agree with the appellant that the cited passage conveys the teaching that inactivation may be carried out with any given detergent or one chosen from a general class of detergents.

6.6 In view of the above, the board has come to the conclusion that the skilled person seeking to provide an alternative to the method disclosed in document D4 had no reason to modify it by introducing virus inactivation by the use of Tween 20.

6.7 Thus the claimed solutions were not obvious to the skilled person when starting from the disclosure in document D4.

Closest prior art document D5

6.8 There was disagreement between the parties as to the disclosure content of document D5.

6.9 In the appellant's view, document D5 in example 3 disclosed a method from which the claimed method differed merely by a detergent virus inactivation step with Tween 20. Specifically, example 3 described in column 6, lines 49 to 56 a method of preparing α1-PI starting from the commercially available product Prolastin. The method involved steps (e), (f) and (g) according to the claims at issue. In turn, Prolastin

was prepared by a method disclosed in each of documents D4, D9, D10 and D11. Such method included steps (a), (c) and (d), as well as the part of step (b) consisting of dilution.

6.10 According to the board's established case law, a prior art document anticipates claimed subject-matter if the latter is directly and unambiguously derivable from that document. An implicit disclosure is one the skilled person would objectively consider as necessarily implied in what is explicit in the document.

6.11 While document D5 does not refer to either of documents D4 and D9 to D11, the appellant rather argued that the skilled person knew from the common general knowledge, as represented by documents D37 to D41, that the method of preparing commercially-available Prolastin was as described in any of those documents. This argument is however not deemed convincing. Firstly, the board is not convinced that the skilled person would necessarily read into the method any additional method steps for the production of Prolastin instead of a method having Prolastin as the input. Secondly, if method steps were implied by the Prolastin, it cannot be said that they would inevitably be those disclosed in any of documents D4, D9, D10 and D11.

6.12 Thus the board comes to the conclusion that the method disclosed in example 3 of document D5 does not implicitly include the steps of PEG precipitation and anion exchange chromatography in addition to the explicitly-disclosed steps of cation exchange chromatography. This being the conclusion of the board, the appellant did not pursue their inventive-step

attack starting from document D5 as closest prior art any further.

7. *Amendments – Extension of protection conferred by the patent – Article 123(3) EPC*

7.1 This objection was put forward in the context of the main request, but applies equally to auxiliary request 1.

7.2 The parties disagreed on the construction of the claim. According to the appellant, the claim allowed for e.g. the forming of an intermediate paste between the precipitation of α1-PI in step (a) and the anion exchange chromatography. Should the board take the view that step (b) immediately followed step (a) in claims 1 and 2 as granted, in other words that the solution resulting from step (a) was the same as that being processed in step (b), then the claims did not allow for additional intermediate steps such as the virus inactivation step. Consequently, the inclusion of a virus inactivation step amounted to an extension of the protection conferred by the patent.

7.3 The issue of whether or not claim 1 allows for the forming of an intermediate paste is not relevant to the present decision and can thus be left undecided. The board came to the view that, due to the word 'comprising', it cannot be concluded that in general further method steps are excluded from the claimed method and that the solution resulting from step (a) is therefore necessarily identical to that being processed in step (b). It follows that the condition on which the appellant's objection is dependent, i.e. that in the claimed method in the granted patent there could be no additional steps between steps (a) and (b), does not

apply. In light of the above, the board sees no reason to find that the introduction of the virus inactivation step led to an extension of the protection conferred by the patent as granted.

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 with the order to maintain the patent on the basis of the claims of auxiliary request 1, filed with the reply to the statement of grounds of appeal, and a description to be adapted thereto.

The Registrar: The Chairman:

I. Aperribay P. de Heij

Decision electronically authenticated