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Datasheet for the decision of 5 March 2020

Case Number: T 1005/15 - 3.3.02

Application Number: 09731947.9

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Language of the proceedings: EN

Title of invention:
Two-stage ultrafiltration/diafiltration

Patent Proprietor:
Grifols Therapeutics Inc.

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 54, 56, 83

Keyword:
Novelty - (yes)
Inventive step - (yes)
Sufficiency of disclosure - (yes)

Decisions cited:
T 0631/06, T 1696/13

Catchword:

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Case Number: T 1005/15 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 5 March 2020

Appellant: (Opponent)	Baxter Healthcare S.A. Thurgauerstrasse 130 8152 Glattpark/Opfikon (CH)
Representative:	Alt, Michael Bird & Bird LLP Maximiliansplatz 22 80333 München (DE)
Respondent: (Patent Proprietor)	Grifols Therapeutics Inc. 4101 Research Commons 79 TW Alexander Drive Research Triangle Park, NC 27709 (US)
Representative:	Durán-Corretjer, S.L.P. Còrsega, 329 (Paseo de Gracia/Diagonal) 08037 Barcelona (ES)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 March 2015 rejecting the opposition filed against European patent No. 2271382 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	P. de Heij

Summary of Facts and Submissions

I. The appeal of the opponent (appellant) lies from the decision of the opposition division to reject the opposition against European patent 2 271 382.

II. The patent was opposed under Article 100(a) (lack of novelty and inventive step) and (b) EPC.

III. During opposition proceedings, *inter alia* the following documents were cited:

D1 WO 2008/157356 A2
D3 US 2006/0051347 A1
D4 McCue J. P. et al., Reviews of Infectious Diseases. Vol. 8, Suppl.4, 1986, pages S374-S381
D7 WO 2004/001007 A2
D14 WO 02/096457 A2
D18 WO 99/64462 A1
D20 Product Data Sheet: "Centrifugal Devices for Ultrafiltration and Microfiltration", 2003
D21 Roe, S. "Protein Purification Techniques", 2001
D23 Sisti, A. M. et al, Vox Sanguinis, 80, 2001, pages 216-224
D24 "Supplementary test report and experimental data", filed by the respondent

IV. With the statement of grounds of appeal the appellant filed the following documents:

D27 US 5,608,038
D28 Declaration of Wolfgang Teschner dated 10 July 2015

V. With the reply to the grounds of appeal the patent proprietor (hereinafter: respondent) filed auxiliary requests 1-7 and *inter alia* the following document:

D29 Declaration of James Rebbeor dated 11 December 2015

VI. With the letter dated 5 April 2016 the appellant filed *inter alia* the following document:

D32 Wang et al., Mol. Pharmaceutics 2015, 12, 4478-4487
D33 US 2008/0160014 A1

VII. A communication of the board pursuant to Article 15(1) RPBA 2007 was sent in preparation of oral proceedings, scheduled in accordance with the corresponding requests of the parties.

VIII. Oral proceedings before the board were held on 5 March 2020.

IX. The requests of the parties relevant to the decision are as follows:

The appellant requests that the contested decision be set aside and that the patent be revoked in its entirety.

Furthermore, it requests to admit documents D28 and D32 and not to admit documents D24 and D29 into appeal proceedings.

The respondent requests dismissal of the appeal, implying maintenance of the patent as granted.

Furthermore, it requests that the decision of the opposition division to admit document D24 into the proceedings be upheld, that document D29 be admitted into the appeal proceedings and that documents D27, D28, D32 and D33 not be admitted into appeal proceedings.

X. Independent claim 1 of the main request reads as follows:

"*1. A method for concentrating a protein of a solution comprising the protein, the method comprising:*

(a) ultrafiltering the solution using a first membrane to form a first retentate solution comprising the protein at a first concentration, wherein the first membrane has a molecular weight cutoff sufficient to retain at least a portion of the protein present in the solution;

(b) diafiltering the first retentate solution with an aqueous solution using the first membrane to form a second retentate solution comprising the protein at about the first concentration;

(c) formulating the second retentate comprising the diafiltered protein with glycine and adjusting the pH; and

(d) ultrafiltering the second retentate solution using a second membrane to form a final retentate solution comprising the protein at a second concentration, wherein the second membrane has a molecular weight cutoff of about twice the molecular weight cutoff of the first membrane,

wherein the second concentration is greater than the first concentration."

XI. The appellant's arguments, insofar as relevant to the present decision, may be summarised as follows:

Main request (claims as granted)

Admittance - Experimental evidence D24, D28 and D29

The decision of the opposition division to admit D24 into the proceedings was to be reversed. Test report D24 lacked *prima facie* relevance and was late filed. The opposition division had applied its discretion under Article 114(2) EPC incorrectly. D29, filed by the respondent with the reply to the statement of grounds of appeal, was *prima facie* lacking relevance and was late filed, and consequently, also was not to be admitted into proceedings.

D28 filed by the appellant was to be admitted into the proceedings as its filing with the statement of grounds of appeal represented the first opportunity for the appellant to react to the filing of D24 by the respondent.

Admittance - D27

D27 was to be admitted into the proceedings as it did not present new facts and evidence, but rather had been filed to demonstrate that the prevention of Immunoglobulin G (IgG) aggregates using glycine was within the routine ability of the skilled person.

Novelty - Articles 100(a) and 54 EPC

The subject-matter of claim 1 lacked novelty over the disclosure in D1.

Inventive step - Articles 100(a) and 56 EPC

D14 was the closest prior art for assessing inventive step of the claimed subject-matter. The distinguishing features of claim 1 with respect to D14 were the addition of glycine in a step c), and the use of a second membrane having a molecular weight cutoff (MWCO) of about twice the MWCO of the first membrane, according to claim 1, step d). The distinguishing features were not linked to a technical effect. The problem was thus the provision of an alternative method for concentrating a protein. The solution provided in claim 1 was obvious in view of one of D4, D5, D6, D7, D10, D18, D23, or D27 and one of D20 or D21.

Alternatively, the subject-matter of claim 1 lacked inventive step starting from either of D3 as closest prior art, combined with one of D7, D18, D23 or D27 and one of D20 or D21, or D1 combined with D7, D20 or D21.

Sufficiency of disclosure - Article 100(b) EPC

The subject-matter of claim 1 was not sufficiently disclosed. The examples in the patent concerned the concentration of a specific protein, IgG, and did not provide sufficient disclosure for the broad definition of claim 1, which was not limited in terms of the protein to be concentrated.

XII. The respondent's arguments, insofar as relevant to the present decision, may be summarised as follows:

Main request (claims as granted)

Admittance - Experimental evidence D24, D28 and D29

The decision of the opposition division to admit D24 into the proceedings was to be upheld. D24 was filed as a direct reaction to the preliminary opinion issued by the opposition division with the summons to oral proceedings and was thus not late filed.

D28 was not to be admitted into appeal proceedings as it was late filed and lacked *prima facie* relevance.

D29 was *prima facie* relevant and was filed as a direct response to the appeal and the late filing of document D28. It was to be admitted into the proceedings.

Admittance - D27

D27 should have been filed in first instance proceedings and lacked *prima facie* relevance. It was not to be admitted into appeal proceedings.

Novelty - Articles 100(a) and 54 EPC

The subject-matter of claim 1 was novel over D1.

Inventive step - Articles 100(a) and 56 EPC

The subject-matter of claim 1 involved an inventive step over D3, which was the closest prior art. Alternatively, even if the skilled person were to start from D14 or D1 as closest prior art, the subject-matter

of claim 1 also involved an inventive step. The distinguishing features of claim 1 with respect to D14 were the addition of glycine in a step c), and the use of a second membrane having a MWCO of about twice the MWCO of the first membrane according to claim 1, step d). D24 and D29 demonstrated that the distinguishing features led to improved protein concentrations. The problem was at least the provision of an alternative method to provide a protein in a high concentration. The solution provided in claim 1 involved an inventive step.

Sufficiency of disclosure - Article 100(b) EPC

In submitting an objection of lack of sufficient disclosure, the onus was on the appellant to raise serious doubts, substantiated by verifiable facts. The appellant had failed to do this, and as a consequence the subject-matter of claim 1 was sufficiently disclosed.

Reasons for the Decision

1. Admittance - Experimental evidence D24, D28 and D29

1.1 The appellant requested that D24 not be admitted into the appeal proceedings. D24 is an experimental report filed by the respondent during opposition proceedings with the letter of 5 December 2014 as evidence of a technical effect underlying granted claim 1. The opposition division decided to admit D24 into the proceedings.

1.2 The appellant submitted that since oral proceedings before the opposition division took place on

8 January 2015, there had been insufficient time for it either to consult with its own experts, or to react by way of conducting and filing appropriate counter-experiments.

1.3 The board decided not to overturn the opposition division's decision to admit D24 into the proceedings. The filing of D24 was in reaction to the preliminary opinion of the opposition division, expressed in the annex to the summons to oral proceedings dated 18 July 2014 (paragraphs 3.4.3 and 3.4.4), that the differentiating features of claim 1 with respect to the closest prior art (then designated as D2) were not linked to any technical effect. However, the board also agrees with the appellant that insufficient time had elapsed between the filing of D24 and the date of oral proceedings to allow the appellant sufficient time to reply to D24, e.g. by filing appropriate counter-tests. Nevertheless, the circumstances in appeal proceedings are different, and this reason is no longer valid in view of the period of time which has since elapsed, and in particular the filing of D28 with the statement of grounds of appeal, which the appellant itself described as "suitable counter-experimentation" (letter of 2 January 2017, paragraph 12).

1.4 Similarly, the board decided to admit D28 into appeal proceedings pursuant to Article 12(4) RPBA 2007. The filing of D28 by the appellant with the statement of grounds of appeal, in view of the filing of D24 shortly before oral proceedings in opposition, was the earliest procedural stage at which an appropriate reaction to the filing of D24 by the respondent was possible.

1.5 Similarly, D29 was filed by the respondent with the reply to the statement of grounds of appeal as a direct

response to the filing of the appellant's tests in D28. Since D29 clearly could not have been filed earlier, the board decided to admit it into proceedings pursuant to Article 12(4) RPBA 2007.

2. Admittance - D27

2.1 D27 was filed by the appellant with the grounds of appeal to "demonstrate that the prevention of IgG aggregates in intravenously tolerable immunoglobulin preparations by means of the osmolarity-reducing effect of glycine was well within the routine ability of the skilled person" and "...confirms that the reduction of viscosity goes along with the reduction of aggregates and the prevention of aggregate formation" (letter of 2 January 2017, paragraph 11).

2.2 However, the appellant failed to provide any valid reason as to why D27 was not or could not have been filed during opposition proceedings. D27 was already known to the appellant as a citation in D7 (page 3, line 13) and therefore should have been submitted as evidence at an earlier stage. Furthermore, the appellant invoked D27 with the purpose of demonstrating that glycine provided for a reduction in osmolarity, and therefore viscosity, and prevented aggregation of the protein. However, firstly the relevant arguments of the respondent (infra) were not based on attributing viscosity - or aggregate-lowering effects to glycine, but rather that glycine led to a higher final protein concentration. Secondly, even if viscosity and aggregation were to be deemed relevant, D27 does not even disclose these properties in association with glycine (D27, column 2, lines 32-37 and column 3, lines 18-33). In view of this, the board decided not to admit

D27 into the proceedings pursuant to Article 12(4) RPBA 2007.

3. Admittance - D32

3.1 The respondent requested not to admit D32 into the proceedings. The board decided to reject this request. Since despite this decision being adverse to the respondent, the appeal was dismissed, there is no need for the board to provide detailed reasons for the decision to admit D32.

Main request (claims as granted)

4. Novelty - Articles 100(a) and 54 EPC

4.1 Claim 1 of the main request - in simplified terms - refers to a method for concentrating a protein of a solution comprising the protein, the method comprising:

(a) ultrafiltering the solution using a first membrane;

(b) diafiltering the first retentate solution with an aqueous solution using the first membrane to form a second retentate solution;

(c) formulating the second retentate comprising the diafiltered protein with glycine and adjusting the pH; and

(d) ultrafiltering the second retentate solution using a second membrane to form a final retentate solution, wherein the second membrane has a molecular weight cutoff of about twice the molecular weight cutoff of the first membrane.

4.2 The appellant submitted that the subject-matter of claim 1 at issue lacked novelty over D1. D1 related to VLA-4 binding antibody formulations and disclosed the preparation of a concentrated antibody formulation (last paragraph of page 26 - fourth paragraph of page 30; table 1 on page 29). Thus, D1 disclosed a first "UF/DF" (ultrafiltration/diafiltration) using a membrane which, in view of the two possibilities provided for the kD value of the membrane, could have a pore size (molecular weight cutoff; hereinafter MWCO) of 10 kD (page 29, second and third columns, third last row; page 29, line 4), corresponding to step a) of claim 1 at issue. "DF", referred to in the "UF/DF" step mentioned above, i.e. a diafiltration step subsequent to the ultrafiltration step ("UF"), corresponded to step b) of claim 1 at issue. Step c) of claim 1 at issue was disclosed on page 27, lines 6-9 which referred to the addition of buffer (which adjusts to a specific pH value), in association with the addition of glycine, disclosed on page 3, lines 10-12. That step c) of claim 1 at issue could take place before step d) was disclosed on page 27, lines 16-20 ("*... polysorbate and buffer ... are added to the phosphate process intermediate to achieve the final desired antibody concentration*"). A second ultrafiltration using a membrane with a pore size of 30 kD (chosen from either 10kD or 30 kD; page 29, line 4), and thus about twice the MWCO of the first membrane, was disclosed in the final paragraph of page 29, and page 27, lines 14-31).

4.3 The view of the board is as follows. D1 fails to disclose the subject-matter of claim 1, at least for the following reasons:

- As set out above, claim 1 requires that "*the second membrane has a molecular weight cutoff of about*

twice the molecular weight cutoff of the first membrane". Although D1 discloses the use of membranes with e.g. 10 kD or 30 kD pore sizes (page 29, final paragraph), it fails to disclose that the first membrane (step a) of claim 1 at issue) has 10kD pore sizes and the second, (step d) of claim 1 at issue), 30kD pore sizes. There is furthermore no implicit nor explicit indication in D1 that two different membranes should be employed in one and the same process, and that the second membrane should have a MWCO greater than the first.

- Even if one were to assume (incorrectly) that D1 disclosed a process where a first membrane with 10kD pore sizes and a second membrane with 30kD pore sizes were applied, the feature of claim 1 quoted above would still not be disclosed. Although the term "about" in claim 1 lacks clarity to a certain extent, the lack of clarity would extend at the most to the boundaries of experimental error in the measurement of the MWCO parameter of a particular membrane. In the present case, a molecular weight cut-off of 30kD is not equivalent to "about twice" the 10kD cut-off, as required by step d) of claim 1 at issue.

- D1 also fails to disclose the formulation of the second retentate with glycine, and adjusting the pH as required by step c) of claim 1 at issue. The passage in D1 referred to by the appellant which addresses the presence of glycine, namely " *... in another embodiment, the composition contained an amino acid, such as glycine*" (page 3, lines 10-12), does so in a different context. The "composition" referred to in this passage is the final composition, and not a second retentate as required

by claim 1 at issue (D1, page 1, lines 19-20). Thus, although the possible presence of a buffer is mentioned (e.g. D1, page 27, table 1, penultimate row; page 3, lines 22-30), there is no disclosure in D1 of the inclusion of glycine therein.

4.4 The subject-matter of claim 1 is consequently novel vis à vis D1.

5. Inventive step - Articles 100(a) and 56 EPC

Choice of closest prior art

5.1 The appellant submitted that the claimed subject-matter lacked inventive step in view of D14, which was the closest prior art, in combination with one of D4, D5, D6, D7, D10, D18, D23 or D27 and one of D20 or D21. Further objections were submitted starting from

- D3 as closest prior art in combination with one of D7, D18, D23 or D27 and one of D20 or D21;
- D1 as closest prior art, in combination with D7, and one of D20 or D21.

5.2 The respondent submitted that the closest prior art was represented by D3.

5.3 In the view of the board, and in line with the opinion of the appellant, since D14, D3 and D1 all concern the preparation of concentrated protein solutions, each of these documents represent a feasible starting point for the skilled person and thus for the assessment of inventive step. In view of the appellant's choice of D14 as closest prior art, discussions during oral proceedings focused on the assessment of inventive step starting from this document. Starting from D3 or D1

(infra), the parties during oral proceedings referred the board to their written submissions.

5.4 In the following, inventive step of claim 1 at issue will be assessed by applying the problem solution approach starting from each document in turn.

D14 as closest prior art - problem solved

5.5 D14 concerns aqueous solutions having a high concentration of therapeutic antibodies and stable liquid formulations based thereon (page 1, first paragraph). The aim of D14 is to provide a liquid antibody formulation which avoids the need for reconstitution of a freeze-dried product before use (page 2, lines 3-7), has a high protein concentration and a low viscosity (page 5, first paragraph). This aim was achieved in D14 by the formulation of the liquid protein solutions with an acidic component (page 4, central paragraph; page 6, third to sixth full paragraphs). The general process of preparation is disclosed in example 7 (page 22). In a first step, the antibody solution is concentrated to an intermediate concentration; in a second step the concentrated solution is diafiltered with aqueous acetic acid containing $MgCl_2$ or $CaCl_2$ and optionally other additives, and in a third step the diafiltered solution is further concentrated to a high concentration by ultrafiltration (page 22, bullet points).

5.6 It is undisputed among the parties that the subject-matter of claim 1 at issue is distinguished from the disclosure in D14 in that the latter does not disclose the formulation of the second retentate with glycine recited in step (c) of claim 1, nor that the ultrafiltration of the second retentate solution is

carried out with a second membrane having a MWCO of about twice the MWCO of the first membrane, as required by claim 1, step d).

5.7 In order to formulate the objective technical problem underlying the subject-matter of claim 1, the effects of these distinguishing features, if any, with respect to the closest prior art must be determined.

5.8 The experimental data on file includes the examples of the patent, D24 and D29 filed by the respondent, and D28 filed by the appellant.

The data in general

5.9 It is to be noted that claim 1 requires that the retentate of the diafiltration step b) is formulated with glycine in a separate and subsequent step c). In this context, the respondent stated that in order for glycine addition and pH adjustment to have an effect, it was not of importance whether it took place in a step (c) according to claim 1 at issue, i.e. after the diafiltration in step b), or whether it was done concurrently with the diafiltration. Rather, it was important only that it was done prior to the second ultrafiltration step d). This was not contested by the appellant, whose own tests in D28 (infra) also involved diafiltration with a glycine buffer at pH 4, and lacked a subsequent step c) according to claim 1 at issue. Hence, both the appellant and the respondent accept and the board has no reason to disagree, that the results of tests demonstrating the effect (or lack thereof) of adding glycine at an adjusted pH *during* the diafiltration step b) will also hold if the addition and adjustment were to be carried out later, i.e. according to claim 1, step c). This viewpoint also

seems reasonable in view of the results set out in tables 5 and 6 of D29 which show effectively no difference in average protein concentrations obtained (20.3% and 20.4% respectively) whether glycine and pH adjustment is carried out with the diafiltration step b) of claim 1 (table 5) or after, according to step c) of claim 1 at issue (table 6). These results are addressed in detail in reference to D29, below. Consequently, the board also sees no reason, nor has there been any argument submitted, as to why this would not be the case.

The data in the patent

5.10 The respondent submitted that in the patent, the technical effect of glycine addition was demonstrated in figure 5 in conjunction with paragraph [0080]. Thus figure 5 showed that while the presence of glycine in the diafiltration step did not have a significant impact on viscosity, it allowed a higher final protein concentration to be reached. According to paragraph [0080], the end point concentration in the graph was reached when the retentate flow in the UF/DF system stopped. According to the respondent's expert present in oral proceedings before the board, this was defined as the point at which the membrane flux slowed to 10 ml/min. This information was undisputed by the appellant.

5.11 The appellant objected to the generality of the data in figure 5 and corresponding paragraph [0080] of the patent - for example, the specific membrane employed was not specified, nor was the concentration of glycine employed or the pH provided. As a consequence, the data in figure 5 could not be relied on. However, in the absence of any counter-evidence demonstrating that the

results shown in figure 5 are not generally applicable, the board sees no reason to doubt the veracity of the data provided. In view of this, it can be accepted that figure 5 of the patent shows that while the presence of glycine in the ultrafiltration step did not have a significant impact on viscosity, it allowed a higher final protein concentration to be achieved.

The data in the respondent's tests D24

5.12 D24 comprises two tests. Table 1 concerns a "comparative example" in which the addition of glycine at pH 4 took place during diafiltration (step b) of claim 1), while in the examples detailed in table 2, glycine addition and pH adjustment was carried out according to step c) of claim 1 at issue. As set out above, both the comparative example and the examples are suitable for demonstrating an effect, despite the comparative example not including a step corresponding to step c) of claim 1. The tests carried out in tables 1 and 2 thus corresponded to the ultrafiltration of step d) of claim 1 at issue. Thus, either a millipore 100kD membrane, a Koch Hollow fibre 100kD membrane or a millipore 50kD membrane are used. It was accepted that the effects shown by the millipore 100kD membrane and the Koch Hollow fibre 100kD membrane were representative of the MWCO feature of claim 1, i.e. of a second membrane having a MWCO of about twice that of the first membrane of step d). Similarly, it was accepted that the millipore 50kD membrane of table 1 was not as required by claim 1. In table 1, the maximum protein concentration achieved after the second ultrafiltration step (d) using either the millipore 100kD membrane, or the Koch Hollow fibre 100kD membrane, is 19.8% +/- 1.2 and 19.2 % +/- 0.9, respectively. Both values are higher than that achieved

using the millipore 50kD membrane (18.4%). Thus, this table demonstrates that using 100kD membranes in the second ultrafiltration, i.e. having an MWCO as required by claim 1, leads to higher protein concentrations than using 50kD membranes as the second membrane, not having an MWCO as required by claim 1.

5.13 The appellant submitted that the results in table 1 of D24 were not attributable only to the different membrane MWCO, but also to the different types of membrane used. D24 for example included a test where a Pall 70kD membrane was used as the second membrane. Why was the Pall 70kD membrane inferior to the 50kD membrane when a linear progression in the improvement of final protein concentration should be expected?

5.14 The board acknowledges that indeed a lower concentration is achieved with the 70kD membrane. However, there is no absolute reason why a linear progression in improved protein concentration should be expected.

The data in the respondent's tests D29

5.15 Table 4 of D29 reports the results of tests in which a millipore 100kD cassette membrane was employed in the second ultrafiltration according to step d) of claim 1 Similarly to the data provided in D24, it was accepted that the effects shown by the millipore 100kD membrane were representative of the MWCO feature of claim 1, i.e. of a second membrane having a MWCO twice of that of the first membrane according to step d).

5.16 In the first three tests reported in table 4 of D29, diafiltration was performed with water only, with no added glycine or pH adjustment. In the final three test

in said table, diafiltration was carried out with 0.2M glycine buffer at pH 4. As set out above, although these tests did not involve the addition of glycine and adjustment of the pH in a separate step c), subsequent to the diafiltration step b), there is no reason to doubt that any effect, if demonstrated for the latter, would also apply to the former. In the tests of table 4, the effect of adding glycine and adjusting the pH is immediately apparent in the results reported: the concentration of protein obtained is clearly higher for the latter three tests.

5.17 Furthermore, as stated above, the last three tests in table 4 are representative of the MWCO feature of claim 1, step d). In contrast, Experiment number 3 in table 1 of D29 applies a millipore 50kD membrane in the second ultrafiltration step. The MWCO in this step is thus not according to claim 1. With the 50kD membrane, a protein concentration of 17.1% is obtained, which is significantly lower than the range of 19.8-22.0% obtained in the last three tests of table 4 using a 100kD membrane (according to claim 1).

5.18 This effect is confirmed by further experiments. Thus, experiment 4 of table 1 using a 50kD membrane in the second ultrafiltration (and thus not according to claim 1), provides a protein concentration of approximately 15.4%, which is lower than the values obtained in the experiments of entries 22 and 24 in table 3 using a 100kD membrane (according to claim 1), namely 18.2% and 18.8%, respectively.

5.19 Similar improvements in final protein concentration are apparent when comparing entry 1 of table 1 (50kD membrane in the second ultrafiltration step, in the presence of glycine at pH 4,; see page 2, penultimate

paragraph) with entries 18 and 21 (100kD membrane in the second ultrafiltration step, in the presence of glycine at pH 4) in table 3. More specifically, the experiment of entry 1 of table 1, with the MWCO feature not being according to claim 1, resulted in a final protein concentration of approximately 17.7%, while the experiments of entries 18 and 21 with the MWCO feature being according to claim 1, resulted in final protein concentrations of 21.2% and 22.9% respectively.

5.20 Finally, table 5 and 6 of D29 concern experiments using a 50kD millipore membrane in the first ultrafiltration, and a Koch 100kD hollow fibre membrane in second ultrafiltration. In the experiments of table 5, diafiltration is carried out with 0.2M glycine buffer at pH 4, while in those of table 6, the post-diafiltered material was formulated with 0.25M glycine and adjusted to pH 4 before transfer to the second ultrafiltration. As set out above, both sets of experiments are suitable for demonstrating an effect related to the addition of glycine and pH adjustment. The average protein concentration obtained in tables 5 and 6 was over 20%, which is superior to e.g. example 1 of table 1 using a 50kD millipore membrane in the second ultrafiltration step (17.7%). Although, as noted by the appellant, D29 does not comprise any comparative examples using a corresponding 50kD Koch hollow fibre membrane in the second ultrafiltration, the fact that a consistently high protein concentration is obtained in tables 5 and 6 compared to the examples of table 1 employing a 50kD millipore membrane serves as a further indicator of the effect of using a second ultrafiltration membrane having a MWCO of about twice the MWCO of the first membrane.

5.21 The appellant additionally submitted that the millipore 100kD membranes used in some of the tests of D29 addressed above were not suitable for the concentration method, since compared to e.g. the Koch 100kD hollow fibre membrane, there were problems with cleaning of the cassettes, due to the necessity to operate at the gel point in order to achieve higher concentrations (D29, page 5, final two paragraphs). However, the fact that the millipore 100kD membrane may pose problems does not detract from the fact that it provides an improvement in protein concentrations obtained, as set out above.

5.22 It has therefore been demonstrated in D29 that the feature of adding glycine and adjusting the pH and the feature of claim 1, step d) wherein the second membrane has a MWCO about twice the first membrane have the effect of increasing the final concentration of protein obtained in the second ultrafiltration step corresponding to step d) of claim 1 at issue. These results are also consistent with those reported in table 1 of D24, addressed above.

5.23 The respondent's data in the patent, D24 and D29 thus show that a higher final protein concentration can be achieved by the addition of glycine as required by claim 1 and by selecting an MWCO of the second membrane as required by claim 1.

The data in the appellant's tests D28

5.24 D28 discloses three ultrafiltration/diafiltration experiments 1-3 all of which were carried out using a membrane having a MWCO of 50kD, both in the first and second ultrafiltration steps (corresponding to steps a) and d) of claim 1; see D28, page 2, penultimate

paragraph). Experiment 1 was performed with no glycine added, in Experiment 2 0.3M glycine was added to the starting material, and in Experiment 3 0.3M glycine was added between the first and second ultrafiltration by way of diafiltration against 0.3M glycine buffer at pH 4 (D28, page 3, final paragraph; table on page 4). In all experiments, concentrations of protein are reported which are superior to those reported in the patent or in the tests D24 or D29 (approximately 24.5% + 1.6% post-wash, 22.9% + 1.5% post-wash, and 22.7% + 0.8% post-wash respectively; tables 2, 4 and 6). D28 does not comprise examples according to claim 1 at issue, in particular having a second ultrafiltration membrane with a MWCO about twice the first membrane.

5.25 According to the appellant, the results provided in D28 could be directly compared with those reported in D24, and showed that very high concentrations could be obtained without using a second membrane having a MWCO about twice the first membrane. Furthermore, the highest concentration reported was in experiment 1, in which no glycine had been added. D28 therefore demonstrated that there was no effect associated with using a second membrane having a MWCO of about twice the first membrane, or with the use of glycine at the pre-second ultrafiltration stage over the absence thereof (D28, pages 7 and 8, ""II. Conclusion").

5.26 The board does not agree. As noted by the respondent, the concentration percentages reported in the examples of D28 are clearly incorrect. Thus, in experiment 1 of D28 the total yield obtained was 106.4% (concentrate plus post-wash), while total yields of 111.6% and 120.9% were reported for experiments 2 and 3 respectively. Since protein clearly cannot be generated during the concentration method, these results show

that the concentrations provided are overstated and erroneous. Since it is not possible, nor has it been proposed by the appellant, to correct these yields, or to reliably compare them relative to each other, they therefore cannot be relied upon to draw any conclusions with regard to protein concentration or yield, and are essentially meaningless.

5.27 Furthermore, the transmembrane pressure applied during the experiments of D28 is in contrast to the pressures applied in the tests submitted by the respondent in D24 and D29 and that applied according to the patent (paragraph [0068]). More specifically, the transmembrane pressure during the experiments in D28 for the (second) ultrafiltration step was 0.35 bar, corresponding to approximately 5 psig (D28, page 3, final paragraph), while in the tests in D24 and D29, the transmembrane pressures varied between 17.5 and 20 psig (see tables in the respective documents). Thus the transmembrane pressure applied in D28 was up to a factor of four less than that applied in the respondent's experiments. Low transmembrane pressure leads to less clogging in membranes, but higher processing times. The differences in transmembrane pressure has the consequence that it is not possible to reliably compare the data in D28 with that in D24 or D29.

5.28 It was conceded by the appellant that differences in transmembrane pressures affect flux rates across membranes and have an influence on membrane clogging. In view of this, not only are the concentrations reported in the examples of D28 unreliable as set out above, but also the examples of D28 are not carried out in the same way as those of D24, in particular with regard to the transmembrane pressure. A comparison with

the data in D24 is therefore not possible. Although, as noted by the appellant, the transmembrane pressure used in the examples of D24 (and D29) was also not consistent, the scale of the variation was minimal (from 17.5 to 20.0 psig) compared to the up to four-fold difference in transmembrane pressures between the examples of D28 and D24. Since the purpose of D28 according to the appellant was to discredit the results provided in D24, the experiments performed therein should have been done under the same conditions as those in D24.

5.29 It follows therefore that no conclusions with regard to the effects of the claimed subject-matter can be drawn from the tests of D28.

5.30 The difference in transmembrane pressures discussed above was addressed by the respondent for the first time during oral proceedings before the board. This was not contested by the respondent. The appellant requested not to admit this submission into the proceedings. The appellant nevertheless indicated that it was prepared to discuss the issue.

5.31 The board views the new focus on the transmembrane pressure and its effect on membrane clogging as a new allegation of fact. It had thus the discretion whether or not to admit the respondent's submission. Since the issue was not complex, and the appellant had declared itself prepared to discuss it, the board decided to admit it into the appeal proceedings.

The data in the patent, D24, D28 and D29 - summary

5.32 It follows from the above considerations that the appellant's data in D28 provides no information with

regard to whether the distinguishing features of claim 1 at issue over D14 provide a technical effect. On the other hand, as set out above, the patent, D24, and in particular D29 provide evidence that glycine addition and pH adjustment in step c) of claim 1 at issue, and the use of a second membrane with a MWCO of about twice the MWCO of the first membrane according to step d) of claim 1 at issue, lead to the isolation of protein in higher final concentrations than if neither feature were present.

The scope of claim 1 at issue

5.33 While the examples in the patent as well as all of the experiments in D24, D28 and D29 concern a method for concentrating a specific protein, Immunoglobulin G (IgG), claim 1 at issue is directed to a method for concentrating a protein, without any limitation to specific proteins or protein families.

5.34 The appellant submitted that any technical effect associated with the distinguishing features over D14, if acknowledged, could only be attributed to a method for concentrating IgG for which examples and comparative data was on file, and would not extend to a method for concentrating all proteins, as recited in claim 1 at issue. D32, a journal article submitted by the appellant with the letter of 5 April 2016, demonstrated that glycine did not have a viscosity-reducing effect on protein JM1. In this context, the appellant submitted that the effect of glycine on improved protein concentration in the second ultrafiltration of claim 1 at issue was attributable to viscosity reduction. Since, according to D32, glycine produced no or negligible viscosity-decreasing on protein JM1 (page 4481, left hand column, lines 16-18,

and figure 2A), it consequently would also not increase the protein concentration obtained in a method for concentrating this protein according to claim 1 at issue.

5.35 However, as submitted by the respondent, the effect being relied on was not a glycine-induced reduction in viscosity, but rather an increase in protein concentration. As set out above, this effect is demonstrated in the tests D24 and D29 submitted by the respondent. Furthermore, as the appellant itself noted, it is apparent from figure 5 of the patent that the presence of glycine does not have a significant effect on viscosity when compared to water. Thus at the same protein concentration depicted in figure 5, for example 180 mg/ml, the viscosity values for water ("DF in H20" and "DF in H2O (dupl)") are in between the values for glycine ("DF in Gly" and "DF in Gly (dupl)"). A rough calculation from the graph of the average viscosity in water on the one hand and glycine on the other provides approximately the same viscosity value. Thus figure 5 of the patent shows that even for IgG, compared to water alone, glycine does not affect the viscosity of the protein solution. It follows from this that the effect of glycine on improving the protein concentration was not attributable to viscosity-reducing properties as alleged by the appellant. Thus, although D32 may show that the addition of glycine does not influence the viscosity of a solution of JM1 protein, this is irrelevant to the question of whether the effect of increasing protein concentration extends to proteins beyond IgG.

5.36 Furthermore, proteins are a specific class of compounds and while there are a vast number of known proteins, they have some properties in common: for example, they

are all macromolecules consisting of long chains of α-amino acids. While it is plausible that the effects addressed above may vary in degree from one protein to another, in the absence of any evidence, there is no reason to doubt that the effects mentioned above would also be displayed by the distinguishing features when applied to the concentration of proteins other than IgG.

5.37 The appellant submitted further arguments that the evidence in D24 and D29 was not sufficient to support the alleged effects across the scope of claim 1, e.g. for different concentrations of glycine, adjusted to different pHs, and in relation to other membranes, since evidence had only been presented for two specific membrane types, namely Millipore and Koch hollow fibre.

5.38 However, as set out above, D24 and in particular D29 provide evidence of an effect both for the addition of glycine and the adjustment in pH according to claim 1, step c) and the feature that the MWCO of the second membrane is about twice that of the first according to claim 1, step d). Although evidence has only been provided for certain specific embodiments falling within the scope of claim 1, the board has no reason to doubt that the same effects would apply to further embodiments. It is established jurisprudence in opposition (appeal) proceedings that each party bears the burden of proof for the facts it alleges. In particular, the burden of proof for an alleged lack of inventive step lies with the opponent. In the present case, as set out above, the opponent has failed to file any evidence which could cast doubt on the effects demonstrated by the respondent.

Problem solved - conclusion

5.39 In view of the foregoing, the effect of the distinguishing features of claim 1 with respect to D14 is that a high final concentration of protein is obtained.

5.40 **The objective technical problem underlying the subject-matter of claim 1 is thus the provision of an alternative method to provide a protein in a high final concentration.**

The problem of providing an "alternative" method

5.41 The appellant disagreed with the board's formulation of the technical problem to include "a high concentration". The problem was rather to be formulated as the provision of an alternative as such. The technical measures distinguishing the subject-matter of the claim from closest prior art D14 had thus to be seen as arbitrary and consequently obvious. The appellant cited case law concerning alternatives to support its position. Thus, in decision T 631/06 (reasons, 2.3.10) the board stated:

"*In a case where the problem to be solved consists merely to provide an alternative, all the information contained in a document is treated equally by the person skilled in the art, notwithstanding whether it is preferred or not, or whether the implementation of some of the said information presents some difficulties. The so called "could-would" approach, applies when the technical problem to be solved relates in the provision of an improvement or in the suppression of disadvantages, not in the provision of an alternative ...*".

5.42 In decision T 1696/13 (reasons, 5.3.1) the board stated:

"*Die Beschwerdeführerin I hatte schriftlich vorgetragen, dass es für den Fachmann im Stand der Technik keinen Hinweis gegeben habe, in Druckschrift (6) nach einer Lösung seiner technischen Aufgabe zu suchen. Daher habe er, entsprechend des "could-would" Ansatzes keine Veranlassung gehabt, spezifisch und zielgerichtet eine aliphatische oder cycloaliphatische Isocyanat-Komponente zur Herstellung des Polyurethan-Elastomers auszuwählen.*

Indessen ist festzustellen, dass der Fachmann, sofern die Aufgabenstellung lediglich in der Bereitstellung einer Alternative besteht, keinen speziellen Hinweis im Stand der Technik benötigt. Er würde vielmehr auf alle in dem jeweiligen technischen Gebiet bekannten Alternativen zurückgreifen. Daher kann dieses Argument der Beschwerdeführerin I nicht durchgreifen."

5.43 The relevant circumstances underlying both of these decisions are however different from those of the present case. The "alternative" in those cases did not require any specific pointer ("would") in the prior art because the selection of the relevant alternative was seen to be an arbitrary choice.

5.44 An analogous scenario in the present case would have presented itself had it been concluded that the distinguishing features over D14 were not linked to a technical effect. In that situation, the selection of said features could have been seen to represent an arbitrary choice from a host of possible solutions, and therefore lack inventive step.

5.45 However, the solution to the objective technical problem provided in claim 1 at issue comprises distinguishing features over D14 which cannot be considered as arbitrary: the implementation in the method of claim 1 of the addition of glycine/pH adjustment and the use of a second membrane having a MWCO of about twice the first membrane, both of which have been demonstrated to lead to higher final protein concentrations than a corresponding method lacking said features (supra).

Obviousness

5.46 The appellant submitted on the one hand that the feature of glycine addition and pH adjustment and on the other hand the feature that the MWCO of the second membrane was about twice that of the first membrane were not linked, and could be addressed separately for the purpose of inventive step. To the appellant's advantage, in the following the board will assume this to be the case.

The feature of glycine addition and pH adjustment

5.47 With regard to this feature, the appellant submitted that the solution provided by claim 1 at issue was obvious in view of D7, D18 or D23.

5.48 Patent document D7 concerns the concentration of antibody preparations by a membrane filtration process (page 1, lines 11-13). In the discussion regarding the prior art, it is stated to be desirable to reduce the viscosity of the antibody preparation, in order to increase the rate of filtration, maximise recovery, and improve ease of handling (D7, page 3, lines 7-11). Also

addressing the prior art, it is stated that "*In order to inhibit aggregation ... a stabilizing additive such as polyol, and/or a viscosity-reducing agent such as a salt or surfactant, is typically added ... see U.S. Patent ...*" (page 3, lines 20-24). In relation to further prior art, it is stated that "*[g]lycine and/or maltose are also used to stabilize antibodies in a highly concentrated antibody antibody solution*". In exploring the efficiency of tangential flow filtration, a commonly used technique to concentrate and diafilter proteins, viscosity of the solution and the formation of aggregates were identified as features which could affect performance (D7, page 20, line 22 - page 21, line 2). Tangential flow filtration is also proposed in the contested patent for diafiltration and ultrafiltration (paragraphs [0043], [0048] and [0055]).

5.49 According to the appellant, the skilled person faced with the technical problem set out above would learn from D7 that glycine, being a stabiliser and thus causing the reduction of aggregates, would improve the efficiency of the tangential flow filtration and thus provide an alternative to the calcium and magnesium salts employed in D14.

5.50 However, the context in which glycine is mentioned in D7 (page 3, lines 31-33) is in relation to the prior art. The aim of D7 is to prepare concentrated antibody preparations that have lowered viscosity and reduced aggregation and are relatively free of additives (page 4, lines 5-8). This is achieved in D7 by employing a specific concentration of acetate or histidine buffer (page 11, lines 3-8). Therefore, D7 rather teaches away from employing glycine. Finally, while it is mentioned in D7 that glycine may be used to stabilise antibodies, there is no disclosure in D7 that using it may

facilitate higher final protein concentrations in a concentration method comprising a second ultrafiltration such as that underlying claim 1.

5.51 Patent document D18 relates to a process for purifying IgG comprising steps which include a step g) of performing a dia/ultrafiltration to concentrate IgG, optionally adding a stabilising agent (D18, page 5, lines 16-17), and a further dia/ultrafiltration step l) (page 6, lines 1-3). Thus, a stabilising agent may be added according to D18 at the pre-second ultrafiltration stage. On page 18 (lines 8-13) it is stated that the IgG product may comprise protein stabilizing agents, among which amino acids such as glycine are included in a list. Accordingly, the appellant argued that D18 would motivate the skilled person to add glycine in step g) according to D18 in order to solve the technical problem set out above.

5.52 The board notes however that the protein stabilising agents referred to in the cited passage (D18, page 18, lines 8-13) are employed post-preparation, to the purified IgG-containing solution (D18, page 17, lines 8-11); this is also evident from the cited passage itself which refers to "the immunoglobulin product". Thus, the stabilising agents mentioned in this passage are not intended for use in step g) of the preparation of D18, i.e. in a step between the first and the second ultrafiltrations according to claim 1 at issue, but rather to the final (already concentrated) product. Nevertheless, the stabilisers relevant to step g) (D18, page 5, lines 16-17), i.e. those that may be added at a stage corresponding to the concentration method according to claim 1 at issue, are disclosed on page 13, lines 1-6 and include glycine in a list. However, despite the suggestion to employ glycine as stabiliser,

there is no indication in D18 that this will lead to higher concentrations in the product isolated from the second ultrafiltration, compared to the case in which glycine was not added. Thus, there is no motivation in D18 for the skilled person to employ glycine in order to solve the problem as set out above.

5.53 Journal article D23 relates to the preparation of lyophilised and liquid intravenous IgG. The process comprises diafiltration of the protein solution with 0.3M glycine at pH 5 and subsequent concentration to ca. 16% by ultrafiltration (D23, page 217, right hand column, lines 2-5). In the context of the optimisation of the ultrafiltration, it was concluded that diafiltration with 0.3M glycine at pH 5 provided the lowest turbidity in the solution (page 219, table 1 and left hand column, final three lines). The appellant submitted that in view of this, it would have been obvious for the skilled person to add glycine at pH 5 to the process of D14 in order to solve the technical problem set out above.

5.54 However, while D23 links lower turbidity to the use of glycine at pH 5, this does not equate to a resultant increase in final concentrations obtained in the ultrafiltration process. Therefore, D23 does not provide the skilled person with any motivation to solve the technical problem underlying claim 1.

5.55 The appellant in addition referred to documents D4, D5, D6, D10 and D27. However, no detailed reasoning was given for the first four documents and document D27 has not been admitted into the proceedings (supra). These documents therefore need not be considered further.

5.56 It follows that the feature of glycine addition and pH adjustment according to claim 1, step c) would not have been obvious to the skilled person faced with the technical problem as set out above.

The feature that the MWCO of the second membrane is about twice the MWCO of the first membrane

5.57 With respect to this feature, the appellant submitted that the solution provided by claim 1 was obvious in view of D20 or D21. D18 was also mentioned as an example of a protein concentration method using IgG wherein two membranes having a differing MWCO were employed.

5.58 D20 is a product data sheet. Table 1 describes typical solute retention characteristics of a series of membrane MWCO values for a list of substances, including IgG. In relation to the choice of MWCO the following is stated (second page, right hand column):

"*In general, a MWCO should be selected that is three to six times smaller than the molecular weight of the protein to be retained ... If flow rate (or processing time) is a major consideration, selection of a membrane with a MWCO toward the lower end of this range (3x) will yield higher flow rates. If recovery is the primary concern, selection of a tighter membrane (6x) will yield maximum recovery (with a slower flow rate)*"

5.59 The appellant submitted that this passage would provide motivation to the skilled person to solve the technical problem by using a second membrane with a MWCO of about twice the first membrane. The board disagrees. The above passage is a general teaching - there is no

indication that two different membranes should be employed having the characteristics of claim 1, step d), in a single concentration method, and it is not in any way derivable therefrom that the technical problem set out above could be solved by this feature.

5.60 Similarly, D21, an article on protein purification techniques, provides general advice on the choice of membrane pore size and the minimisation of membrane resistance (page 73, 5.4.1; page 112-115, "Ultrafiltration"; page 124, 3.2.1 "Optimization", and page 125, (e)). There is however no teaching nor pointer in D21 that a higher protein concentration can be achieved specifically by using a second membrane with a MWCO of about twice that of the first membrane.

5.61 In a further argument the appellant submitted that the preparation of concentrated IgG solution using two ultrafiltration membranes having different MWCO was already known from D18. Indeed, D18 in example 1, discloses the use of a 30kD MWCO membrane in the dia/ ultrafiltration step 5 (page 24) and a 100kD membrane in the ultrafiltration of step 7 (page 25). Leaving aside that 100kD cannot be considered as "about twice" 30kD, D18 nevertheless provides no indication that such a set-up would provide an advantage with respect to the final protein concentration obtained.

5.62 Consequently, the feature that the second ultrafiltration membrane has a MWCO of about twice the MWCO of the first membrane would not have been obvious to the skilled person faced with the technical problem as set out above.

Conclusion - inventive step starting from D14

5.63 It follows from the foregoing that starting at D14, the skilled person with a view to solving the above-mentioned problem, would not have arrived at the subject-matter of claim 1 at issue without exercising inventive step.

D3 as closest prior art

5.64 In an alternative (although not preferred) approach, the appellant submitted in written proceedings that D3 could also serve as a feasible starting point for the skilled person.

Problem solved

5.65 D3 relates to a process for the concentration of antibodies including a first ultrafiltration, a subsequent diafiltration, and a second ultrafiltration (paragraph [0006]). D3 sets out to improve this process (paragraphs [0003] and [0004]), and achieves this by carrying out one or more of the filtration steps at elevated temperature (paragraphs [0006] and [0045]; claim 1). Glycine is mentioned in D3 only in the context of being a stabilising excipient from which the preparation of the invention is preferably free (paragraph [0072]).

5.66 It is undisputed that the distinguishing features of claim 1 over D3 are the same as those over D14, supra (statement of grounds of appeal, paragraph 167).

5.67 The appellant submitted that the distinguishing features are not linked to a technical effect, and that the solution to the technical problem of providing an

alternative method for concentrating protein was within the routine ability of the skilled person, in particular in view of D7, D18 or D23 (for glycine addition and pH addition), and D20 or D21 (for the MWCO feature of claim 1, step d)).

5.68 However, for the same reasons as set out above with respect to D14, the objective technical problem is the provision of an alternative method to provide a protein in a high final concentration. As also set out above, the solution to the problem is not arbitrary, and none of the prior art cited in combination with D3 provides a teaching or a pointer which would lead the skilled person to the subject-matter of claim 1 at issue.

5.69 It follows that starting at D3, the skilled person, with a view to solving the above-mentioned problem, would not have arrived at the subject-matter of claim 1 at issue without exercising inventive step.

D1 as closest prior art

5.70 In a further alternative (although not preferred) approach, the appellant submitted in written proceedings that D1 could also serve as a feasible starting point for the skilled person.

5.71 It is undisputed that D1 could only serve as state of the art under Article 54(2) EPC, as alleged by the appellant, if the priority date were to be deemed invalid. The respondent submitted that the priority date was valid. Nevertheless, to the benefit of the appellant, it will be assumed for the purpose of the following that the priority is invalid and consequently, that D1 may be invoked in the assessment of inventive step pursuant to Article 56 EPC.

5.72 The disclosure of D1 is addressed above in relation to novelty. The arguments of the appellant according to which the claimed subject-matter lacked inventive step over D1 start from the assumption that D1 disclosed all features of claim 1 with the exception of a second membrane having a MWCO of about twice the first membrane (statement of grounds of appeal, paragraph 192). However, as set out above, D1 also fails to disclose the formulation of the second retentate with glycine, and adjusting the pH as required by step c) of claim 1 at issue. As set forth above with respect to D14 and D3, a technical effect has been demonstrated for both of these features. The objective technical problem is consequently again the provision of an alternative method to provide a protein in a high final concentration.

5.73 For the same reasons as provided above starting from either of D14 or D3, the solution to the problem provided in claim 1 at issue involves an inventive step starting from D1, in combination with any of D7, D20 or D21.

5.74 It follows that starting at D1, the skilled person, with a view to solving the above-mentioned problem, would not have arrived at the subject-matter of claim 1 at issue without exercising inventive step.

5.75 In view of this conclusion, there was no need for the board to investigate the validity of the priority date in the contested patent.

Inventive step - conclusions

5.76 In view of the above considerations, the subject-matter of claim 1 involves an inventive step. This conclusion also applies by analogy to dependent claims 2-15.

6. Sufficiency of disclosure - Article 100(b) EPC

6.1 The appellant submitted that the subject-matter defined in claim 1 of the main request was insufficiently disclosed. The examples in the patent concerned solely the concentration of a specific IgG, which did not provide sufficient disclosure for the broad definition of claim 1 which was directed to "a method for concentrating a protein", without limitation. Given the lack of guidance in the patent, the skilled person did not know how to adjust the various parameters which were necessary for a successful concentration process, for example whether control of aggregation can be achieved, to which pH value to adjust, how much glycine to add and which specific membranes to employ when the protein was not IgG. Evidence for the position of the appellant was provided by D4, D16 and D32. According to D4, IgG was unstable at pH 7 (D4, page S381, left hand column, lines 8-10). D16 demonstrated that it was not possible to ultrafilter casein under pH 8.5 due to precipitation (abstract), and D32 demonstrated that glycine did not affect the viscosity of JM1 protein (D32, page 4481, left hand column).

6.2 It is established jurisprudence that a successful objection of lack of sufficiency of disclosure presupposes that there are serious doubts, substantiated by verifiable facts. In order to establish insufficiency of disclosure in inter-partes proceedings, the burden of proof is upon an opponent to

establish, on the balance of probabilities, that a skilled person reading the patent and using his common general knowledge, would be unable to carry out the invention. The mere fact that a claim is broad is not in itself a ground for considering that the requirement of sufficient disclosure is not fulfilled.

6.3 In the present case, the appellant's arguments are not substantiated by suitable evidence. The skilled person is aware of the fact that different proteins have differing properties. The mere fact that many proteins exist is not sufficient proof that the claimed method will not be universally applicable. No evidence has been presented that the skilled person would be unable to adjust the necessary conditions of the claimed method to suit a specific protein in accordance with the guidance provided in the patent (paragraphs [0022] - [0056]), and in view of his common general knowledge. The evidence cited by the appellant cannot change this conclusion: while IgG may be unstable at pH 7 (D4), or casein may precipitate under pH 8.5 (D16), this does not mean that the skilled person is unable, through routine experimentation, to adjust the conditions of the claimed method accordingly. Furthermore, as set out above, that according to D32 glycine did not affect the viscosity of JM1 protein is irrelevant to the question of whether it would be possible to concentrate JM1 via the method of claim 1.

6.4 Consequently, the invention defined in claim 1 at issue is sufficiently disclosed.

Further requests

7. The respondent has requested not to admit document D33. As this document turned out not to be relevant for the

present decision, its admittance into proceedings did not need to be considered.

Conclusion

The main request (patent as granted) is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated