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Datasheet for the decision of 15 June 2021

Case Number: T 2437/18 - 3.3.04

Application Number: 10747134.4

Publication Number: 2467399

IPC: C07K14/755

Language of the proceedings: EN

Title of invention:
Purification of vWF for increased removal of non-lipid enveloped viruses

Patent Proprietors:
Baxalta Incorporated
Baxalta GmbH

Opponent:
Strawman Limited

Headword:
Removal of non-lipid enveloped viruses/BAXALTA

Relevant legal provisions:
EPC Art. 83, 100(c), 123(2)
RPBA 2020 Art. 13

Keyword:
Sufficiency of disclosure (no)
Added subject-matter (yes)
Admittance (no)

Decisions cited:
G 0001/03, T 0727/00

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Case Number: T 2437/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 June 2021

Appellants: (Patent Proprietors)	Baxalta Incorporated 1200 Lakeside Drive Bannockburn, IL 60015 (US)
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Respondent: (Opponent)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 11 July 2018 concerning maintenance of the European Patent No. 2467399 in amended form**

Composition of the Board:

Chair	M. Blasi
Members:	A. Schmitt
	R. Morawetz

Summary of Facts and Submissions

I. The appeal of the patent proprietors (appellants) lies from the opposition division's interlocutory decision that European patent No. 2 467 399 (patent), as amended in the form of auxiliary request 8, and the invention to which it relates meet the requirements of the EPC.

II. The patent, entitled "*Purification of vWF for increased removal of non-lipid enveloped viruses*", was granted on European patent application No. 10 747 134.4, which had been filed as an international application under the PCT (application) published as WO 2011/022657.

Claims 5 and 14 of the application read as follows:

"5. A method for removing a non-lipid enveloped virus from a protein-containing solution comprising:
applying the solution to a cation exchange resin at a pH higher than the isoelectric point of the protein;
and washing the cation exchange resin with a first wash buffer at a pH higher than the isoelectric point of the protein applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is equal to or lower than the first wash buffer.

14. A method for removing a non-lipid enveloped virus from a VWF-containing solution comprising:
applying the solution to a cation exchange resin,
washing the cation exchange resin with a first wash buffer at a pH higher than the pH of the solution applied to the cation exchange resin; and

washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is equal to or lower than the first wash buffer."

Claims 1, 5, 12 and 14 as granted read as follows:

"1. A method for removing a non-lipid enveloped virus from a protein-containing solution comprising:
applying the solution to a cation exchange resin at a pH higher than the isoelectric point of the protein; and washing the cation exchange resin with a wash buffer to form an eluate, said wash buffer having a pH that is equal to or lower than the solution applied to the cation exchange resin,
wherein the protein in the solution is a polypeptide having a molecular mass of at least 150 kilodaltons, and whereby the non-lipid enveloped virus is removed from the protein-containing solution.

5. A method for removing a non-lipid enveloped virus from a protein-containing solution comprising:
applying the solution to a cation exchange resin at a pH higher than the isoelectric point of the protein; and washing the cation exchange resin with a first wash buffer at a pH higher than the isoelectric point of the protein applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is equal to or lower than the first wash buffer,
wherein the protein in the solution is a polypeptide having a molecular mass of at least 150 kilodaltons, and whereby the non-lipid enveloped virus is removed from the protein-containing solution.

12. A method for removing a non-lipid enveloped virus from a van Willebrand Factor (VWF)-containing solution comprising:
applying the solution to a cation exchange resin at a pH higher than the isoelectric point of VWF; and
washing the cation exchange resin with a first wash buffer to form an eluate, said first wash buffer having a pH that is equal to or lower than the solution applied to the cation exchange resin.

14. A method for removing a non-lipid enveloped virus from a VWF-containing solution comprising:
applying the solution to a cation exchange resin at a pH higher than the isoelectric point of VWF; and
washing the cation exchange resin with a first wash buffer at a pH higher than the isoelectric point of VWF applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is equal to or lower than the first wash buffer, and whereby the non-lipid enveloped virus is removed from the VWF-containing solution."

III. An opposition had been filed against the patent in its entirety. The opposition proceedings were based on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) in Article 100(a) EPC and on the grounds in Article 100(b) and (c) EPC.

IV. In the decision under appeal, the opposition division considered, *inter alia*, that the patent did not disclose the invention as defined in claims 1, 5, 12 and 14 as granted in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The finding of a lack of sufficiency of disclosure also applied to the invention claimed in

auxiliary requests 1 to 7. It was, *inter alia*, evident from the disclosure in the patent that no tangible removal of NLEV could be achieved when the cation exchange chromatography was carried out at neutral pH or at pH 8.0 and that, therefore, embodiments were covered by the claim which did not permit a tangible removal of NLEV. In line with decision G 1/03 (OJ EPO 2004, 413), this resulted in a lack of sufficiency of disclosure. Auxiliary request 8 was considered to meet the requirements of the EPC.

Claims 1, 5, 12 and 14 of auxiliary request 1 considered by the opposition division were identical to claims 1, 5, 12 and 14 as granted, respectively (see section II.), except that the expression "equal to or" had been deleted from the definition of the wash buffer to form an eluate in claims 1 and 12 and the definition of the first eluant in claims 5 and 14.

Claims 1, 5, 12 and 14 of auxiliary request 2 considered by the opposition division read as follows:

"1. Use of a cation exchange resin for removing a non-lipid enveloped virus from a protein-containing solution in a method comprising:
applying the solution to the cation exchange resin at a pH higher than the isoelectric point of the protein; and washing the cation exchange resin with a wash buffer to form an eluate, said wash buffer having a pH that is equal to or lower than the solution applied to the cation exchange resin,
wherein the protein in the solution is a polypeptide having a molecular mass of at least 150 kilodaltons, and whereby the non-lipid enveloped virus is removed from the protein-containing solution.

5. Use of a cation exchange resin for removing a non-lipid enveloped virus from a protein-containing solution in a method comprising:
applying the solution to the cation exchange resin at a pH higher than the isoelectric point of the protein; and washing the cation exchange resin with a first wash buffer at a pH higher than the isoelectric point of the protein applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is equal to or lower than the first wash buffer, wherein the protein in the solution is a polypeptide having a molecular mass of at least 150 kilodaltons, and whereby the non-lipid enveloped virus is removed from the protein-containing solution.

12. Use of a cation exchange resin for removing a non-lipid enveloped virus from a von Willebrand Factor (VWF)-containing solution in a method comprising:
applying the solution to the cation exchange resin at a pH higher than the isoelectric point of VWF; and
washing the cation exchange resin with a first wash buffer to form an eluate, said first wash buffer having a pH that is equal to or lower than the solution applied to the cation exchange resin.

14. Use of a cation exchange resin for removing a non-lipid enveloped virus from a VWF-containing solution in a method comprising:
applying the solution to the cation exchange resin at a pH higher than the isoelectric point of VWF; and
washing the cation exchange resin with a first wash buffer at a pH higher than the isoelectric point of VWF applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH

that is equal to or lower than the first wash buffer, and whereby the non-lipid enveloped virus is removed from the VWF-containing solution."

Claims 1, 5, 12 and 14 of auxiliary request 3 were identical to claims 1, 5, 12 and 14 of auxiliary request 2, respectively, except that the expression "equal to or" had been deleted from the definition of the wash buffer to form an eluate in claims 1 and 12 and the definition of the first eluant in claims 5 and 14.

Claims 1, 3, 8 and 10 of auxiliary request 4 were identical to claims 1, 5, 12 and 14 of the patent as granted, respectively (see section II.), except that in claims 1 and 8 the feature "at a pH higher" (than the isoelectric point of the protein) had been replaced with the feature "at a pH 2.5 pH units or more pH units higher" and that claims 3 and 10 contained the additional feature "wherein the pH of the solution applied to the cation exchange resin and/or the pH of the first wash buffer is 2.5 pH units or more pH units higher than the isoelectric point of the protein".

Claims 1, 3, 8 and 10 of auxiliary request 5 were identical to claims 1, 5, 12 and 14 of auxiliary request 1, respectively, except that they contained the same amendments as claims 1, 3, 8 and 10 of auxiliary request 4, respectively (see above).

Claims 1, 3, 8 and 10 of auxiliary request 6 were identical to claims 1, 5, 12 and 14 of auxiliary request 2, respectively, except that they contained the same amendments as claims 1, 3, 8 and 10 of auxiliary request 4, respectively (see above).

Claims 1, 3, 8 and 10 of auxiliary request 7 were identical to claims 1, 5, 12 and 14 of auxiliary request 3, respectively, except that they contained the same amendments as claims 1, 3, 8 and 10 of auxiliary request 4, respectively (see above).

The independent claims of auxiliary request 8 filed at the oral proceedings before the opposition division and underlying the decision under appeal read as follows:

"1. A method for removing a non-lipid enveloped virus from a protein-containing solution comprising:
applying the solution to a cation exchange resin at a pH 3.0 pH units or more pH units higher than the isoelectric point of the protein; and
washing the cation exchange resin with a wash buffer to form an eluate, said wash buffer having a pH that is lower than the solution applied to the cation exchange resin,
wherein the protein in the solution is a polypeptide having a molecular mass of at least 150 kilodaltons, and whereby the non-lipid enveloped virus is removed from the protein-containing solution.

5. A method for removing a non-lipid enveloped virus from a von Willebrand Factor (VWF)-containing solution comprising:
applying the solution to a cation exchange resin at a pH 3.0 pH units or more pH units higher than the isoelectric point of VWF; and
washing the cation exchange resin with a first wash buffer to form an eluate, said first wash buffer having a pH that is lower than the solution applied to the cation exchange resin."

V. With the statement of grounds of appeal, the appellants submitted sets of claims of auxiliary requests I to XII. The sets of claims of auxiliary requests I to VII and XII are identical to the sets of claims of auxiliary requests 1 to 8 considered by the opposition division, respectively (see section IV.). The sets of claims of auxiliary requests VIII to XI are new to the proceedings.

Claims 1, 3, 8 and 10 of auxiliary request VIII are identical to claims 1, 5, 12 and 14 of the patent as granted, respectively (see section II.), except that in claims 1 and 8, the feature "at a pH higher" (than the isoelectric point of the protein) has been replaced with the feature "at a pH 2.6 pH units or more pH units higher" and that claims 3 and 10 contain the additional feature "wherein the pH of the solution applied to the cation exchange resin and/or the pH of the first wash buffer is 2.6 pH units or more pH units higher than the isoelectric point of the protein".

Claims 1, 3, 8 and 10 of auxiliary request IX are identical to claims 1, 5, 12 and 14 of auxiliary request 1 considered by the opposition division, respectively (see section IV.), except that they contain the same amendments as claims 1, 3, 8 and 10 of auxiliary request VIII, respectively (see above).

Claims 1, 3, 8 and 10 of auxiliary request X are identical to claims 1, 5, 12 and 14 of auxiliary request 2 considered by the opposition division, respectively (see section IV.), except that they contain the same amendments as claims 1, 3, 8 and 10 of auxiliary request VIII, respectively (see above).

Claims 3 and 10 of auxiliary request XI are identical to claims 5 and 14 of auxiliary request 3 considered by the opposition division, respectively (see section IV.), except that they contain the same amendments as claims 3 and 10 of auxiliary request VIII, respectively (see above).

VI. The opponent (respondent) replied to the appeal by the letter of 3 April 2019 and submitted, *inter alia*, arguments supporting its view that the invention as defined in claims 1, 5, 12 and 14 as granted was not disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Auxiliary requests I to VII and IX to XI were likewise objected to for lack of sufficient disclosure. Furthermore, claims 3 and 10 of auxiliary request VIII comprised added subject-matter and the comments regarding auxiliary requests I, II and VIII applied to each of auxiliary requests IX, X and XI which combined the amendments of earlier claim requests.

VII. By letter dated 18 December 2019, the appellants submitted sets of claims of auxiliary requests IXA, XIA and XIB.

Claims 1, 3, 8 and 10 of auxiliary requests IXA and XIA are identical to claims 1, 3, 8 and 10 of auxiliary requests IX and XI, respectively (see section V.), except that in claims 3 and 10 of auxiliary requests IXA and XIA, the term "and/or" has been replaced by "or".

Claims 1 and 8 of auxiliary request XIB are identical to claims 1 and 5 of auxiliary request 8 underlying the

decision under appeal (see section IV.). Claims 2, 3, 9 and 10 of auxiliary request XIB read as follows:

"2. A method for removing a non-lipid enveloped virus from a protein-containing solution comprising:
applying the solution to a cation exchange resin,
washing the cation exchange resin with a first wash buffer at a pH higher than the pH of the solution applied to the cation exchange resin, wherein the pH of the first wash buffer is at least 3.0 pH units above the isoelectric point of the protein applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is lower than the first wash buffer,
wherein the protein in the solution is a polypeptide having a molecular mass of at least 150 kilodaltons, and whereby the non-lipid enveloped virus is removed from the protein-containing solution.

3. A method for removing a non-lipid enveloped virus from a protein-containing solution comprising:
applying the solution to a cation exchange resin at a pH higher than the isoelectric point of the protein; and washing the cation exchange resin with a first wash buffer at a pH higher than the isoelectric point of the protein applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is lower than the first wash buffer,
wherein the protein in the solution is a polypeptide having a molecular mass of at least 150 kilodaltons, and whereby the non-lipid enveloped virus is removed from the protein-containing solution,
wherein the pH of the solution applied to the cation exchange resin or the pH of the first wash buffer is

3.0 pH units or more pH units higher than the isoelectric point of the protein.

9. A method for removing a non-lipid enveloped virus from a VWF-containing solution comprising:
applying the solution to a cation exchange resin,
washing the cation exchange resin with a first wash buffer at a pH higher than the pH of the solution applied to the cation exchange resin, wherein the pH of the first wash buffer is at least 3.0 pH units above the isoelectric point of the protein applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is lower than the first wash buffer.

10. A method for removing a non-lipid enveloped virus from a VWF-containing solution comprising:
applying the solution to a cation exchange resin at a pH higher than the isoelectric point of VWF; and
washing the cation exchange resin with a first wash buffer at a pH higher than the isoelectric point of VWF applied to the cation exchange resin; and
washing the cation exchange resin with a second wash buffer to form an eluate, said first eluant having a pH that is lower than the first wash buffer, and whereby the non-lipid enveloped virus is removed from the VWF-containing solution,
wherein the pH of the solution applied to the cation exchange resin or the pH of the first wash buffer is 3.0 units or more pH units higher than the isoelectric point of the protein."

VIII. The board appointed oral proceedings, according to the parties' requests, and issued a communication pursuant to Article 15(1) RPBA 2020.

IX. By letter dated 24 May 2021, the respondent requested that auxiliary requests IXA, XIA and XIB not be admitted into the proceedings and stated that it maintained all requests and objections raised thus far.

X. Oral proceedings were held on 15 June 2021 by videoconference with the consent of both parties. During the oral proceedings, the board, *inter alia*, admitted auxiliary requests VIII to XI, IXA and XIA into the appeal proceedings. At the end of the oral proceedings, the Chair announced the board's decision.

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

D1 WHO Technical Report, Series No. 924, 2004, Annex 4, Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products

D2 US 6,465,624 B1 (15 October 2002)

D4 EP 0 934 748 A2 (14 December 1998)

D5 EMA Guidelines 1996, Note for guidance on virus validation studies: The design, contribution and interpretation of studies validating the inactivation and removal of viruses

D6 A. Johnston and W. Adcock, Biotechnology and Genetic Engineering Reviews 17, 2000, 37-70

D13 Declaration on Example 3 of document D2 (23 November 2017)

XII. The appellants' submissions relevant to the decision are summarised as follows.

Main request (patent as granted)
Claim construction - Claims 1, 5, 12 and 14
Meaning of the phrase "removing a non-lipid enveloped virus"

In the context of separation methods as recited in the claims of the patent, the phrase "removing a non-lipid enveloped virus from a protein-containing solution" did not mean "eliminating" non-lipid enveloped virus (NLEV) from the solution. Rather, it was used as synonym for "reducing" the NLEV in the solution. This meaning was supported by the disclosure in the patent, which referred in paragraph [0007] to "removal or inactivation" and in paragraph [0008] to "reduction and/or inactivation", showing that the terms "removal" and "reduction" were used interchangeably in the patent.

The meaning of "tangible" NLEV removal or reduction concerned clarity and not sufficiency of disclosure. It only meant that the NLEV reduction had to be measurable. No other meaning could be derived from the patent or the prior art. Documents D1, D5 and D6 could not serve as evidence that NLEV had to be reduced by the claimed methods by a particular $\log_{10}$ reduction factor because these documents referred to the reduction of NLEV in a different context and as a regulatory requirement, which was not generally applicable.

From Example 5 of the patent, no $\log_{10}$ reduction factor could be derived either because the methods carried out in this example did not fall within the scope of the

claims. The elution buffer used in this example had a higher pH than the washing and the loading buffers and not an equal to or lower one as recited in the claims. Moreover, Table 5 of Example 5 did not indicate how far below 1 the observed $\log_{10}$ reduction factors were. Therefore, the disclosure in paragraph [0094] of the patent could not be interpreted such that a tangible removal of NLEV required a minimal $\log_{10}$ reduction factor of more than 1.

Consequently, since the claimed subject-matter did not require that a particular $\log_{10}$ reduction factor of NLEV be achieved, the skilled person only needed to assess whether a measurable removal of NLEV was achieved, but not to what extent. Hence, a reduction factor of less than 1 $\log_{10}$ constituted a tangible removal of NLEV, especially in view of the difficulty inherent in removing NLEVs from solutions (see paragraphs [0007] and [0008] of the patent and document D1, paragraph bridging pages 163 and 164).

Sufficiency of disclosure (Article 100(b) EPC)
Claims 1, 5, 12 and 14

Considering this meaning of the phrase "removing NLEV from a protein-containing solution", Example 1 demonstrated that a tangible removal of NLEV was achieved when the loading and washing of the cation exchange resin was performed at pH 8.0 and 9.0. This was evident from Table 1, which showed that at pH 8.0, the $\log_{10}$ reduction factor for the virus MMV was 0.9, i.e. the virus concentration was reduced almost eightfold. Paragraph [0068] of the patent merely expressed that the reduction at pH 8.0 was not as large as when the method was performed at pH 9.0, which led to a removal factor of more than 2 $\log_{10}$ (see also

Table 1). Moreover, document D13 disclosed that it was possible to achieve an NLEV reduction factor of more than 1 $\log_{10}$ with loading and washing solutions having pH 8.0 (page 5). This further supported that a tangible NLEV removal could be achieved under these conditions.

Examples 3 and 4 of the patent also disclosed experimental conditions under which a tangible removal of NLEV could be achieved. The experimental conditions taught in Examples 1, 3 and 4 and Table 1 of the patent therefore served as proof of principle and rendered it plausible that the other claimed pH schemes, for which no direct experimental data were present, also led to removal of NLEV. The invention as defined in claims 1, 5, 12 and 14 was therefore sufficiently disclosed in the patent.

Furthermore, since the removal of NLEV was a functional feature of the claim, pH values which did not achieve this purpose were anyhow not covered by the claims. It was not challenging for the skilled person to find out which pH values were not covered since the patent provided sufficient guidance in its examples on which embodiments led to a removal of NLEV and, in paragraph [0026], which did not.

Consequently, even if embodiments achieving a removal of NLEV with a $\log_{10}$ reduction factor of less than 1 were considered non-working embodiments, it could not be concluded that there was a lack of sufficiency of disclosure. In accordance with decision G 1/03 of the Enlarged Board of Appeal (OJ EPO 2004, 413), under the circumstances presented in the patent, the inclusion of non-working embodiments in the scope of the claim was acceptable (see Reasons, 2.5.2).

Auxiliary request I
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 5, 12 and 14

In line with established case law of the boards of appeal, the burden of proof was on the respondent to demonstrate that the claimed invention could not be carried out across the claimed scope. The respondent, however, had not submitted any evidence for its allegation but only relied on data disclosed in the patent allegedly disclosing, in Example 1, non-working embodiments. In these embodiments, the loading, washing and elution buffers all had pH 8.0 (see Table 1 of the patent).

In the methods recited in claims 1, 5, 12 and 14 of auxiliary request I, the wash buffer used to form an eluate had a lower pH value than the solution used in the preceding step of the claimed methods (the loading buffer in claims 1 and 12; the first wash buffer in claims 5 and 14). Therefore, the embodiments disclosed in Table 1 of the patent that allegedly did not work were not within the scope of the claims of auxiliary request I and could hence not serve as evidence that the claimed invention could not be carried out without undue burden. No other evidence had been presented by the respondent to support its objection.

The purification methods disclosed in Examples 3 and 4 of the patent fell within the scope of the claims of auxiliary request I (the loading of the cation exchange resin was performed at pH 9.0, whereas the elution buffer had pH 7.5). These examples demonstrated that the claimed methods could be carried out by the skilled person without undue burden. In view of this evidence provided in the patent and the lack of any evidence to

the contrary submitted by the respondent, there were no serious doubts substantiated by verifiable facts that the claimed invention could be carried out across the entire claimed scope.

Auxiliary requests II and III
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 5, 12 and 14

The appellants did not submit any arguments on sufficiency of disclosure of the invention as defined in claims 1, 5, 12 and 14 of auxiliary requests II and III.

Auxiliary request IV
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

The methods of claims 1, 3, 8 and 10 of auxiliary request IV required that the solution applied to the cation exchange resin (and/or the pH of the first wash buffer in claims 3 and 10) was 2.5 pH units or more pH units higher than the isoelectric point of the protein. Consequently, since the isoelectric point of VWF was 5.5 to 6.0, these claims did not encompass the purification of VWF with buffers that had a neutral pH.

Purification of VWF at pH 8.0 led to tangible removal of NLEV, as evident from Example 1 (Table 1) of the patent and confirmed by document D13 (page 5). Consequently, the invention as defined in claims 1, 3, 8 and 10 of auxiliary request IV was sufficiently disclosed in the patent.

Auxiliary requests V, VI and VII
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

The appellants did not submit any arguments on sufficiency of disclosure of the invention as defined in claims 1, 3, 8 and 10 of auxiliary requests V, VI and VII.

Auxiliary request VIII
Amendments (Article 123(2) EPC) - claims 3 and 10

The basis for claims 3 and 10 of auxiliary request VIII could be found in claims 5 and 14 and paragraphs [0016], [0017], [0064] and [0067] of the application. Since claims 5 and 14 of the application disclosed that the pH value of the first wash buffer and the eluant could be the same, choosing the pH of the wash buffer or the eluant determined the pH of the other. Thus, selections from two independent lists were not necessary to arrive at the subject-matter of claims 3 and 10 of auxiliary request VIII. Furthermore, in the embodiments of Example 1 (Table 1), the buffers for loading and washing the cation exchange resin had the same pH value including pH 8.0 and 9.0. Example 1 thus firstly provided a pointer to selecting a loading and a washing buffer having the same pH and secondly a pointer to selecting solutions having pH 8.1, which was the next logical step following buffers having pH 8.0 towards those having pH 9.0.

Auxiliary requests IX, X and XI
Amendments (Article 123(2) EPC) - claims 3 and 10

The appellants did not submit any arguments on added subject-matter in claims 3 and 10 of auxiliary requests IX, X and XI.

Auxiliary requests IXA and XIA
Admittance of objections under Article 83 EPC to claims 1, 3, 8 and 10 (Article 13(2) RPBA 2020)

The objections of insufficient disclosure raised for these requests should not be admitted into the proceedings. During the written appeal proceedings, the respondent had not argued that the invention as defined in claims 1, 3, 8 and 10 of auxiliary requests IX and XI was not sufficiently disclosed, even though these auxiliary requests had been submitted in December 2019. It was irrelevant that similar objections had been brought forward in the respondent's reply to the statement of grounds of appeal to the claims of auxiliary request VIII because auxiliary requests IX and XI were further, different claim requests that should have been addressed separately.

Thus, no objections under Article 83 EPC had been raised on auxiliary requests IX and IX which could be regarded as relevant for the invention as defined in the claims of auxiliary requests IXA and XIA.

The respondent's objections under Article 83 EPC to the invention as defined in claims 1, 3, 8 and 10 of auxiliary requests IXA and XIA were thus submitted for the first time during the oral proceedings before the board and should therefore not be admitted.

Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

The claimed methods or uses did not encompass embodiments where the solution applied to the cation exchange resin had pH 8.0. Therefore, the alleged non-working embodiment of Example 1 of the patent was not encompassed within the scope of the claims, indeed none of the allegedly non-working embodiments disclosed in the patent fell within the scope of the claims. The patent could therefore not be used as evidence for an alleged lack of enablement, and the respondent had not submitted any evidence demonstrating that embodiments falling within the scope of the claims of auxiliary requests IXA and IXA did not result in removal of NLEV.

The patent showed that when solutions having pH 8.0 were used, a NLEV $\log_{10}$ removal factor of 0.9 was achieved, i.e. a $\log_{10}$ removal factor of almost 1, the alleged threshold for a tangible removal of NLEV. Furthermore, the patent demonstrated that a tangible removal of NLEV was achieved when using solutions having pH 9.0 (Examples 1, 3 and 4). In view of this teaching in the patent, there was a big difference between pH 8.0 and pH 8.1. Indeed, the difference between pH 8.0 and pH 8.1 was sufficiently large to make it credible for the skilled person that a tangible removal could be achieved when using solutions at pH 8.1.

Auxiliary request XIB
Admittance (Article 13(1) RPBA 2020)

This request should be admitted into the proceedings. The set of claims for this request was submitted at the same time as auxiliary requests IXA and XIA, which had

been submitted in direct response to objections on added subject-matter raised by the respondent in its reply to the appellants' statement of grounds of appeal. It was based on auxiliary request XII submitted with the statement of grounds of appeal, i.e. on the claims considered allowable by the opposition division. It contained additional independent claims 2, 3, 9 and 10 which were based on claims comprised in preceding claim requests and contained the same limitations as inserted in claim 1 of auxiliary request XII.

XIII. The respondent's submissions relevant to the decision are summarised as follows.

Main request (patent as granted)
Claim construction - Claims 1, 5, 12 and 14
Meaning of the phrase "removing a non-lipid enveloped virus"

Claims 1, 5, 12 and 14 were directed to methods for removing an NLEV from a protein- (or VWF-) containing solution. Thus, the removal of the NLEV was a purpose-limited technical effect of the claimed methods which had to be achieved by the recited method steps over the entire claimed range. In the context of the claimed methods, "removing NLEV" meant that the removal had to be "tangible". In the relevant technical field of producing therapeutic protein solutions, the $\log_{10}$ reduction factor for a tangible removal of NLEV must be at least greater than 1. This was evident from documents D6, D1 and D5 and the patent, which disclosed that smaller reduction factors were not significant (see Example 1, Table 1, paragraph [0068] and Example 5, Table 5, paragraph [0094]).

Example 5 served as evidence for the meaning of a "tangible" removal in the patent, despite the fact that the elution buffer used in Example 5 had a pH value that was not within the claimed range. The pH value of the elution buffer was irrelevant for NLEV removal because only the loading and/or washing steps were responsible for achieving removal of the NLEV from the protein-containing solution. Hence, only the pH values of the loading and/or the washing buffers were relevant for NLEV removal (see paragraphs [0011], [0012], [0013], [0014] and lines 1 to 2 and 30 to 31 of page 14 of the patent).

Sufficiency of disclosure (Article 100(b) EPC)
Claims 1, 5, 12 and 14

In view of this meaning of the expression "removing NLEV", it was evident from paragraph [0026] and Examples 1 and 5 of the patent that there were embodiments falling within the scope of the claims that did not result in a tangible NLEV removal, i.e. non-working embodiments. Paragraph [0026] disclosed that purification of VWF using cation exchange chromatography at a neutral pH, which was higher than the isoelectric point of VWF (5.5 to 6.0), could not remove NLEV. The same teaching was present in Example 5 (Table 5). Example 1 furthermore demonstrated that no tangible removal of NLEV could be achieved when the loading and washing of the cation exchange resin was performed at pH 8.0, experimental conditions that also fell within the scope of the claims (see Table 1 and paragraph [0068]).

In accordance with decision G 1/03 of the Enlarged Board of Appeal (OJ EPO 2004, 413), the inclusion of non-working embodiments was only of no harm if there

was a large number of conceivable alternatives and the patent contained sufficient information on the relevant criteria for finding appropriate alternatives over the claimed range with reasonable effort (Reasons, 2.5.2).

These conditions were, however, not fulfilled in the case at hand. The only working embodiment disclosed in the patent was the removal of NLEV from a VWF-containing solution using a loading and a washing buffer that both had pH 9.0, which is at least 3 pH units above the isoelectric point of VWF (see Examples 1, 3 and 4). The use of buffers having a single pH value for the purification of a single protein, which had unique localised charge characteristics and was therefore not representative of other large proteins, neither constituted a large number of conceivable alternatives nor provided sufficient information on the relevant criteria for finding appropriate alternatives over the claimed range.

From the teaching of the patent, the skilled person therefore did not know how NLEV could be removed from a protein-containing solution across the pH values falling within the scope of claims 1, 5, 12 and 14. The skilled person could therefore not carry out the claimed methods across the claimed scope without undue burden.

Auxiliary request I
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 5, 12 and 14

The only difference in the subject-matter of claims 1, 5, 12 and 14 of auxiliary request I compared to that of claims 1, 5, 12 and 14 of the main request was that the

pH of the "wash buffer to form an eluate", i.e. the elution buffer, had to be "lower" (instead of "equal to or lower") than the pH of the solution applied to the cation exchange resin (claims 1 and 12) or the first wash buffer (claims 5 and 14). This amendment hence only concerned the step of eluting the protein from the cation exchange resin, which was not relevant for the removal of NLEV from the protein-containing solution.

It was irrelevant whether the embodiments disclosed in Example 1 fell precisely within the scope of the claims because the critical features, i.e. the pH values of the loading and/or washing buffer, were the same as in the claims of the main request. Therefore, the data reported for load and wash at pH 8.0 in Table 1 of the patent were still applicable to this claim. Therefore, the same considerations as for the claims of the main request applied, and the patent alone provided serious doubts substantiated by verifiable facts that the claimed methods could be carried out across the entire claimed scope.

In view of these considerations and the evidence provided in the patent, the respondent had discharged its burden of proof. Under these circumstances, the appellants had to demonstrate that the claimed method could be carried out across the claimed scope (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, III.G.5.2.1, last paragraph on page 776 and III.G.5.2.2, page 778, second paragraph). Since the appellants failed to demonstrate this, there was lack of sufficiency of disclosure.

Auxiliary requests II and III
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 5, 12 and 14

The same objections raised under Article 83 EPC to the invention defined in claims 1, 5, 12 and 14 of auxiliary request I applied to the invention defined in claims 1, 5, 12 and 14 of auxiliary requests II and III.

Auxiliary request IV
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

The data in Example 1 (Table 1) of the patent showed that no tangible removal of VWF could be achieved when the buffers used for loading and/or washing the cation exchange resin had a pH of 8.0, i.e. a pH that was 2.5 pH units higher than the isoelectric point of VWF. This non-working embodiment was therefore comprised within the scope of claims 1, 3, 8 and 10 of auxiliary request IV, and thus the invention as defined in claims 1, 3, 8 and 10 of auxiliary request IV was not sufficiently disclosed in the patent.

Auxiliary requests V, VI and VII
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

The same objections raised under Article 83 EPC to the invention defined in claims 1, 3, 8 and 10 of auxiliary request IV applied to the invention defined in claims 1, 3, 8 and 10 of auxiliary requests V, VI and VII.

Auxiliary request VIII
Amendments (Article 123(2) EPC) - claims 3 and 10

Claims 3 and 10 of auxiliary request VIII contained subject-matter that extended beyond the content of the application as filed since the value "2.6" for the pH of the solution applied to the cation exchange resin and the first wash buffer had to be selected from two different lists, which each comprised a large number of possible alternative pH values (see paragraphs [0064] and [0067] of the application). Moreover, the application lacked a pointer towards pH value 2.6, which was arbitrarily selected from these two lists. Paragraphs [0016] and [0017] could not be used as basis for amending claim 3 and 10 since they related to methods different to those recited in these claims.

Auxiliary requests IX, X, XI
Amendments (Article 123(2) EPC) - claims 3 and 10

Claims 3 and 10 of auxiliary requests IX, X and XI contained subject-matter extending beyond the content of the application as filed for the same reasons as claims 3 and 10 of auxiliary request VIII.

Auxiliary requests IXA and XIA
Admittance of objections to claims 1, 3, 8 and 10 (Article 13(2) RPBA 2020)

The objections of insufficient disclosure against these claim requests should be admitted into the proceedings. In the reply to the appellants' statement of grounds of appeal (in due time after the appellants' submission of their claim requests pursued on appeal), an objection had been raised under Article 83 EPC to the invention defined in the claims of auxiliary request VIII newly

filed on appeal (see page 22 of the reply). It was furthermore indicated in the reply that auxiliary requests IX and XI combined the amendments of auxiliary requests I and II with those of auxiliary request VIII, respectively, and that, therefore, the comments on each of these earlier requests equally applied to each of auxiliary requests IX and XI (see section 3.7.4 on page 23).

Hence, the respondent had raised, in a timely manner, objections under Article 83 EPC to the sets of claims of auxiliary requests IX and XI. These objections also applied to auxiliary requests IXA and XIA submitted by the appellants after the response to the appellants' statement of grounds of appeal since these claims only differed in the replacement of the term "and/or" by "or" in claims 3 and 10. These objections were therefore not late filed and should hence be admitted into the appeal proceedings.

Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

The invention defined in claims 1, 3, 8 and 10 of auxiliary requests IXA and XIA was not sufficiently disclosed in the patent. The data in Example 1 of the patent (Table 1 and paragraph [68]) demonstrated that no tangible removal of NLEV from a VWF-containing solution could be achieved when the load and wash buffers for the cation exchange resin had pH 8.0, i.e. a pH value that was 2.5 pH units higher than the isoelectric point of the protein (VWF).

Since the method could not be carried out using load and wash buffers having pH 8.0 and that in the sole working example of the patent the load and wash buffers

both had pH 9.0, the skilled person had serious doubts that the claimed methods could be carried out with buffers having pH 8.1, i.e. a pH that was only 0.1 units higher than a pH that did not work.

The burden of proof was on the appellants to demonstrate that the methods could be carried out. The appellants, however, did not provide any evidence for their allegations.

Auxiliary request XIB
Admittance (Article 13(1) RPBA 2020)

Auxiliary request XIB should not be admitted into the proceedings. The re-introduction of independent claims deleted during the opposition proceedings, i.e. had been given up then, was not an amendment submitted in response to any objection of the respondent. Moreover, the appellants had not provided any convincing argument why they had submitted auxiliary request XIB so late in the appeal proceedings and not with their statement of grounds of appeal.

XIV. The parties' requests relevant for the decision are summarised as follows.

The appellants requested that the decision under appeal be set aside and that the opposition be rejected, i.e. the patent be maintained as granted (main request), or, alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests I to VII, all filed during the proceedings before the opposition division and resubmitted with the statement of grounds of appeal, or, further alternatively, on the basis of one of the

sets of auxiliary requests VIII to XI, all submitted with the statement of grounds of appeal,
or, further alternatively, on the basis of auxiliary request IXA, XIA, XIB, all submitted with the letter dated 18 December 2019, with auxiliary request IXA being ranked below auxiliary request IX and auxiliary requests XIA and XIB - in this order - being ranked below auxiliary request XI.
The request of maintenance of the patent in amended form as considered allowable by the opposition division (auxiliary request XII) was confirmed to be maintained.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

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

Main request (patent as granted)
Claim construction - Claims 1, 5, 12 and 14
Meaning of the phrase "removing a non-lipid enveloped virus"

2. Claims 1, 5, 12 and 14 as granted are directed to methods for "removing" a non-lipid enveloped virus (NLEV) from a protein (von Willebrand Factor (VWF))-containing solution by cation exchange chromatography (see section II.). The meaning of the expression "removing" NLEV used in these claims is relevant for determining the subject-matter of the claim. It is therefore also relevant for the assessment of sufficiency of disclosure and not only a matter of clarity, as argued by the appellants.

3. The relevant technical field for the patent is the preparation of protein compositions for therapeutic use (see paragraph [0007] of the patent). The removal of contaminating viruses from therapeutic protein preparations is important because viral contaminations could have "*serious clinical consequences*" (see paragraph [0008] of the patent). As a consequence, regulatory guidelines on the reduction and/or inactivation of both lipid enveloped and non-lipid enveloped viruses were developed (see paragraph [0008] of the patent). Document D6, a review article on the use of chromatography to manufacture purer and safer plasma products refers to such regulatory guidelines. The opposition division was therefore right that document D6 is relevant for the claimed methods. Document D6 discloses that a $\log_{10}$ reduction "*less than or equal to 1 is not significant*" (see the first full paragraph on page 54).

4. The teaching of document D6 that a "significant" NLEV removal must by achieved when preparing protein compositions for therapeutic use is furthermore confirmed in the patent, which uses the expressions "*significant removal rate*" and "*significantly reduced*" when assessing the NLEV removal achieved under different experimental conditions (see paragraphs [0067], [0068], [0087] and [0091] of the patent; see also points 6. and 7. below). The skilled person would therefore not consider that, as argued by the appellants, the claimed methods did not require any minimum $\log_{10}$ reduction factor to achieve the claimed NLEV "removal" - which would mean, in the extreme, that the removal of a single virus particle was comprised within the claimed methods for "removing" NLEV from a protein-containing solution.

5. Moreover, as set out in more detail in points 6. to 11. below, the patent also discloses which NLEV reduction factors are considered "significant" (or insignificant) and which experimental conditions achieve such a "significant" (or insignificant) NLEV removal. The board is therefore not persuaded, either, by the appellants' argument that no requirement for a minimal NLEV removal factor could be derived from the patent.

6. In Example 1 of the patent, various parameters of the VWF purification method were altered and their effect on removal or reduction of NLEV was assessed (see paragraphs [0064] to [0070] and Table 1 of the patent). The results are interpreted in the patent such that *"moderate changes in the process parameters (modification of conductivity, pH 8.0 and additives to wash buffers) did not result in a significant improvement of the MMV removal rates"*, whereas conducting the loading and washing steps at pH 9.0 "*reproducibly resulted in a significant removal rate of more than 2 logs for MMV as well as REO virus*" (see paragraph [0068]). Hence, according to the disclosure in paragraph [0068] of the patent, a removal factor of more than 2 $\log_{10}$ is "significant" whereas a removal factor of 0.9 $\log_{10}$, achieved with washing and loading buffers having pH 8.0 (see Table 1), is not.

7. Examples 3 and 4 of the patent confirm that according to the patent, a removal factor of more than 2 $\log_{10}$ is significant. They disclose that purification of recombinant VWF by cation exchange chromatography at pH 9.0 "*significantly reduced the binding of the virus particles to the resin*" such that a "*virus removal capacity of 2 logs*" could be obtained (see

paragraphs [0087] and [0091] and Tables 3 and 4 of the patent).

8. Example 5 of the patent discloses the purification of recombinant VWF by cation exchange chromatography at "*neutral pH*" (pH 6.5; see paragraphs [0093] and [0094]). It is concluded that "*[t]he results in Table 5 show that by applying the standard purification procedure for VWF on UNOsphere S the removal capacity for non-enveloped viruses was insufficient for the different model viruses tested to claim a robust chromatographic step for removal of non-lipid enveloped viruses*" (see paragraph [0094]). Table 5 discloses $\log_{10}$ reduction factors of "<1" for three of the tested viruses and 1.8 for two of the tested viruses. Consequently, Example 5 supports the teaching of Example 1 of the patent that a $\log_{10}$ reduction factor smaller than 1 is not significant.

9. Example 5 of the patent can be used to assess the meaning of a "significant" NLEV removal as defined in the patent. Although the purification protocol of Example 5 does not fall within the scope of the claimed methods, the only difference is that the elution buffer used in Example 5 has a pH higher than the pH of the loading or washing buffer, and not, as recited in the claims, a pH equal to or lower than the pH of these buffers.

10. However, the elution step does not have any influence on NLEV removal from the protein-containing solution because it only serves to release the purified protein from the cation exchange resin after the removal has been accomplished in the loading and/or washing steps (see paragraphs [0011], [0013] and [0014] of the patent). Hence, to assess under which conditions a

significant NLEV removal is achieved, only the pH value of the loading and/or the washing buffer is relevant but not that of the elution buffer. This view is supported by Example 1 of the patent, where only the pH of the loading and washing buffers was altered, whereas the elution of the bound VWF was performed under identical neutral conditions (see Table 1 and paragraph [0068]), and by paragraph [0087] of the patent, which discloses that the "*increased pH during the loading and wash phase significantly reduced the binding of the virus particles to the resin but retained full binding of the product VWF*" (emphasis added by the board). A corresponding passage can also be found in paragraph [0091] of the patent.

11. The patent thus teaches in Examples 1, 3, 4 and 5 that significant removal of NLEV is achieved when it is reduced in the protein-containing solution by a factor of at least 2 $\log_{10}$ whereas a $\log_{10}$ reduction factor of less than 1 is not significant. The appellants' view that any NLEV removal that was measurable was tangible and thus significant cannot therefore be accepted.

12. In view of the above, the board is also not persuaded by the appellants' argument that because of the inherent difficulty to remove NLEVs from solutions, a $\log_{10}$ reduction factor of less than 1 also constituted a significant removal of NLEV. A potential difficulty in achieving a task does not have any bearing on determining under which conditions this task is considered to be achieved.

13. The opposition division was therefore correct in finding that the removal of NLEV achieved by the claimed methods must be "tangible" (i.e. significant)

and that a $\log_{10}$ reduction factor of less than 1 does not qualify as such a "significant" NLEV removal.

Sufficiency of disclosure (Article 100(b) EPC)
Claims 1, 5, 12 and 14

14. Paragraph [0026] of the patent discloses that previous methods of purifying VWF using cation exchange chromatography, which "*were performed at neutral pH [,]... had no capacity to remove non-lipid enveloped viruses*". I.e. according to the patent, no significant removal of NLEV occurs when the loading and washing steps are performed at neutral pH. This is confirmed in Example 5 of the patent, where the loading and washing steps were performed at pH 6.5 (see Table 5 and points 8. to 10. above).

15. Moreover, Example 1 of the patent discloses that no significant removal of NLEV from a VWF-containing solution is achieved when the loading and the washing of the cation exchange chromatography is performed with buffers having pH 8.0 (see point 6. above).
Document D13, which discloses a cation exchange protocol carried out at pH 8.0 and, according to the appellants, a significant removal of NLEV using buffers having pH 8.0, has no bearing on this finding because the experimental study of document D13 was carried out using the cation exchange protocol of document D2's Example 3 and not that of the patent (see the first paragraph on page 2 of document D13).

16. Since the isoelectric point of VWF is 5.5 to 6.0 (see e.g. document D2, line 45 of column 3), each of these pH values (6.5, 7.0 and 8.0) is higher than the isoelectric point of VWF. Consequently, serious doubts supported by verifiable facts that removal of NLEV can

be achieved for all buffer conditions recited in claims 1, 5, 12 and 14 as granted can be derived from the patent. Consequently, the appellants' argument that Examples 1, 3 and 4 disclosed conditions which led to a removal of NLEV from a protein-containing solution and served as proof of principle that it was plausible that also the other pH schemes comprised within the scope of the claims lead to removal of NLEV must fail.

17. Furthermore, it is indeed correct that the purpose of the methods recited in the claims (removal of NLEV) is a functional technical feature of the claims. However, the consequence of reciting this functional feature in the claims is not, as argued by the appellants, that the pH values of the loading and/or the washing buffers are implicitly limited to those pH values which can achieve NLEV removal and that, therefore, non-working embodiments are not included within the scope of the claims and a lack of sufficiency of disclosure could not arise. Instead, explicitly reciting the purpose in the claim as a functional technical feature has the consequence that this functional feature (NLEV removal) must be achieved for all protein-containing solutions and all buffer conditions recited in the claims. If this is not the case, "non-working embodiments" are included within the claim. This may result in the finding of lack of reproducibility - and thus lack of sufficiency of disclosure - of the claimed invention (see decision G 1/03 of the Enlarged Board of Appeal, OJ EPO 2004, 413; Reasons, 2.5.2.).

18. The inclusion of "non-working embodiments" within a claim is only of no harm if there is "*a large number of conceivable alternatives*" and the patent contains "*sufficient information on the relevant criteria for finding appropriate alternatives over the claimed range*

with reasonable effort" (see G 1/03, cited above).

19. These conditions are, however, not fulfilled in the case at hand. The patent only discloses successful removal of NLEV from a protein solution at a single pH condition for both the loading and the washing buffers, namely pH 9.0 (see Examples 1, 3 and 4; and Tables 1, 3 and 4) and for a single protein (recombinant VWF), i.e. it does not disclose "*a large number of conceivable alternatives*".

20. Moreover, since only a single working example is disclosed and it is further shown in the patent that a variety of pH conditions for the different buffers used in the claimed methods do not allow removal of NLEV from a protein-containing solution, the patent lacks guidance on how NLEV could be removed using buffers having pH values across the pH ranges recited in claims 1, 5, 12 and 14. Furthermore, the patent does not provide any teaching or suggestion on how to alter the methods it discloses to achieve the claimed effect. The skilled person thus would have to experimentally assess each possible combination of pH values for each of the buffers to find out which buffer combinations might work. This does not amount to reasonable effort as referred to in G 1/03 (cited above).

21. The board therefore holds that the patent does not provide sufficient guidance to enable the skilled person to achieve the functional technical feature expressed in claims 1, 5, 12 and 14 (NLEV removal). Absent any relevant common general knowledge, the skilled person is not able to practice the invention as defined in these claims across the recited pH ranges without undue burden. The invention as defined in claims 1, 5, 12 and 14 as granted is not disclosed in

the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art within the meaning of Article 100(b) EPC.

Auxiliary request I
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 5, 12 and 14

22. The parties referred in their submissions to the patent and not the application as filed. The board ascertained that there is no difference in the disclosure in the relevant passages of the application and the patent and, therefore, saw no need to correct the parties' references. In claims 1 and 12, the wash buffer for forming an eluate has a pH lower than that of the solution applied to the cation exchange resin, this solution having a pH higher than the isoelectric point of the protein (claim 1) or VWF (claim 12). In claims 5 and 14, the first eluant has a pH lower than that of the first wash buffer (see section IV). According to the appellants, the embodiments of Example 1 of the patent or application hence did not fall anymore within the scope of the claims because in this example all buffers had the same pH.

23. However, firstly, as set out above (see point 10.), Table 1 of Example 1 only refers to the pH of the load and the wash buffers (see the column "Parameter" of Table 1), and paragraph [0068] of the patent discloses that "*[e]lution of the bound rVWF is performed under neutral conditions*". Moreover, only the high pH of the loading and/or the washing buffers is responsible for NLEV removal but not the pH of the elution buffer used to release the purified protein from the cation exchange resin (see paragraphs [0011], [0013] and [0014] of the patent and points 2. and 10. above).

The board therefore agrees with the respondent that claims 1, 5, 12 and 14 still embrace embodiments in which the buffer in the load and the wash steps have a pH 8.0. Accordingly, the load and wash data reported for pH 8.0 in Table 1 of the patent are still applicable to these claims.

24. Therefore, the same considerations on sufficiency of disclosure as for claims 1, 5, 12 and 14 of the main request apply to claims 1, 5, 12 and 14 of auxiliary request I (see points 15. to 21. above). The invention defined in claims 1, 5, 12 and 14 of auxiliary request I is therefore not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art within the meaning of Article 83 EPC.

Auxiliary requests II and III
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 5, 12 and 14

25. Claims 1, 5, 12 and 14 of each of auxiliary requests II and III are formulated as use claims. The pH values of the solution applied to the cation exchange resin and the wash buffer(s) recited in claims 1, 5, 12 and 14 of auxiliary requests II and III are identical to those recited in claims 1, 5, 12 and 14 of the main request and auxiliary request 1, respectively (see section IV). Moreover, the parties presented no additional arguments for auxiliary requests II and III.

26. Therefore, the same considerations on sufficiency of disclosure as for claims 1, 5, 12 and 14 of the main request apply to claims 1, 5, 12 and 14 of auxiliary request II (see points 14. to 21. above), and the same considerations on sufficiency of disclosure as for

claims 1, 5, 12 and 14 of auxiliary request I apply to claims 1, 5, 12 and 14 of auxiliary request III (see points 22. to 24. above). Consequently, the invention defined in claims 1, 3, 8 and 10 of auxiliary requests II and III is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art within the meaning of Article 83 EPC.

Auxiliary request IV
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

27. Since the isoelectric point of VWF is 5.5 to 6.0 (see e.g. document D2, line 45 of column 3), the methods of claims 1, 3, 8 and 10 encompass non-working embodiments in which the protein is VWF and the pH of the solution applied to the cation exchange resin and/or the wash buffer is 8.0 (see point 15. above). This results in a lack of sufficiency of disclosure of the invention defined in these claims (see points 16. to 21. above). Consequently, the invention defined in claims 1, 3, 8 and 10 of auxiliary request IV is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art within the meaning of Article 83 EPC.

Auxiliary requests V, VI and VII
Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

28. Claims 1, 3, 8 and 10 of auxiliary requests V, VI and VI are identical to claims 1, 5, 12 and 14 of auxiliary requests I, II and III, respectively, except that they contain the same amendments as claims 1, 3, 8 and 10 of auxiliary request IV, respectively (see section V.).

Moreover, the parties presented no additional arguments for auxiliary requests V, VI and VII. Therefore, the same considerations on sufficiency of disclosure as for claims 1, 3, 8 and 10 of auxiliary request IV apply to claims 1, 3, 8 and 10 of auxiliary requests V, VI and VII (see points 27. above). Consequently, the invention defined in claims 1, 3, 8 and 10 of auxiliary requests V, VI and VII is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art within the meaning of Article 83 EPC.

Auxiliary request VIII
Amendments (Article 123(2) EPC) - claims 3 and 10

29. The subject-matter of claim 3 of auxiliary request VIII comprises the subject-matter of claim 5 of the application (see section II.) and the feature that "the pH of the solution applied to the cation exchange resin and/or the pH of the first wash buffer is 2.6 pH units or more pH units higher than the isoelectric point of the protein" (emphasis added by the board). The same additional features are recited in claim 10 of auxiliary request VIII, which comprises the subject-matter of claim 14 of the application (see section II.).

30. According to the appellants, paragraphs [0016], [0017], [0064] and [0067] of the application provided a basis for these features. However, firstly, paragraph [0016] concerns an aspect of the method disclosed in paragraph [0015] different from the methods of claims 5 and 14 of the application and can therefore not be combined with these. The same is true for the disclosure in paragraph [0017] on yet a further method. For this reason alone, paragraphs [0016] and [0017]

cannot serve as a basis for claims 3 and 10 of auxiliary request VIII.

31. Secondly, paragraph [0064] discloses a list of 22 pH values that the solution applied to the cation exchange resin may have, including that the pH of the solution is about 2.6 pH units or more above the isoelectric point of the protein. Paragraph [0067] discloses a list of 50 pH values for the first wash buffer, including that the pH value of the first wash buffer is about 2.6 pH units or more above the isoelectric point of the protein. Thus, paragraphs [0064] and [0067] disclose the pH values of the solution and the first wash buffer recited in the claims in two separate lists but not in combination. The same is also true for the disclosure in paragraphs [0016] and [0017].

32. Under established case law of the boards of appeal, a combination of features singled out by selection from two different lists is not considered to be disclosed in an application unless the application contains a clear pointer to such a combination (see e.g. decision T 727/00 (Reasons 1.1.4) cited in the Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, II.E.1.6.2).

33. In the case at hand, the application does not provide a pointer to a pH value 2.6 pH units higher than the isoelectric point of the protein for either the applied solution or the first wash buffer. The examples of the application concern a single protein (VWF) and experiments with solutions having pH 8.0 (Example 1) or pH 9.0 (Example 1, 3 and 4), i.e. pH values 2.5 or 3.0 pH units higher than the isoelectric point of this protein. The disclosure of solutions having two pH values (8.0 and 9.0) does not point to solutions having

pH 8.1 or any other pH value between these two disclosed values. Indeed, the application does not contain any disclosure which supports the appellants' argument that pH 8.1 was "the next logical step" after pH 8.0. The two pH values for the loading and the washing solution recited in claims 3 and 10 are thus arbitrarily chosen from the two lists in paragraphs [0064] and [0067].

34. Furthermore, neither claim 5 nor the examples comprise clear pointers towards the use of the same pH for the loading and the washing buffers. Claim 5 discloses that the second buffer for forming an eluate could have the same pH as the first wash buffer but not the loading buffer. In Examples 1, 3 and 4, loading and washing buffers with the same pH are used. However, the examples only disclose methods using two specific pH values (pH 8.0 and 9.0). This is not a clear pointer towards a combination of any other arbitrary pH value from the lists in paragraphs [0064] and [0067].

35. Methods in which "the pH of the solution applied to the cation exchange resin and the pH of the first wash buffer is 2.6 pH units or more pH units higher than the isoelectric point of the protein" are therefore not directly and unambiguously disclosed in the application as filed. Claims 3 and 10 of auxiliary request VIII thus contain subject-matter which extends beyond the content of the application within the meaning of Article 123(2) EPC.

Auxiliary requests IX, X, XI
Amendments (Article 123(2) EPC) - claims 3 and 10

36. The same considerations on added subject-matter as in claims 3 and 10 of auxiliary request VIII apply to

claims 3 and 10 of auxiliary requests IX, X and XI, which also comprise the feature that "the pH of the solution applied to the cation exchange resin and/or the pH of the first wash buffer is 2.6 pH units or more pH units higher than the isoelectric point of the protein" (see section V. above). Claims 3 and 10 of auxiliary requests IX, X and XI therefore also contain subject-matter which extends beyond the content of the application within the meaning of Article 123(2) EPC.

Auxiliary requests IXA and XIA
Admittance of objections under Article 83 EPC to claims 1, 3, 8 and 10 (Article 13(2) RPBA 2020)

37. With the statement of grounds of appeal, the appellants submitted sets of claims of auxiliary requests I to XII. Auxiliary requests VIII to IX were new to the proceedings (see section V.). In its reply to the appellants' statement of grounds of appeal, the respondent submitted an objection under Article 83 EPC to the invention defined in the claims of auxiliary request VIII (see page 22 of the reply) and indicated that the same objection applied to auxiliary requests IX and XI (see section 3.7.4 on page 23). Hence, the respondent's objection under Article 83 EPC to the invention claimed in auxiliary requests IX and XI was raised in a timely manner.

38. The sets of claims of auxiliary requests IXA and XIA were submitted by the appellants in reaction to the respondent's objections under Article 123(2) EPC to claims 3 and 10 of auxiliary requests IX and XI and only differ from the sets of claims of auxiliary requests IX and XI in the replacement of the term "and/or" by "or" in claims 3 and 10 (see section VII.).

39. The board does not consider that maintaining the objection under Article 83 EPC raised in the reply to the appeal for the claim requests submitted to address a different issue - here Article 123(2) EPC - represents an amendment of the respondent's appeal case in substance. However, the objection itself was explicitly raised for auxiliary requests IXA and XIA only at the oral proceedings before the board and therefore constitutes an amendment as compared to the respondent's earlier submissions on these claim requests in which this objection had not been explicitly raised.

40. Under Article 13(2) RPBA 2020, applicable to the current case pursuant to Article 24 and Article 25 RPBA 2020, the board has discretion over whether to admit an amendment to a party's appeal case made after the summons to oral proceedings.

41. Considering that the respondent, in the letter of 24 May 2021, had requested - and presented arguments to this effect - that auxiliary requests IXA and XIA not be admitted into the appeal proceedings and subsequently stated that all objections raised thus far would be maintained, it could not have come as a surprise that the same objections under Article 83 EPC would be raised against the invention as defined in the claims of auxiliary requests IXA and XIA that had been timely raised for the invention as defined in the claims of auxiliary requests IX and XI once auxiliary requests IXA and XIA were to be addressed in substance. The issues to be discussed at the oral proceedings remained the same, adding no further complexity, and the appellants could be expected to be able to deal with the changed situation at the oral proceedings. The

appellants submitted nothing which would have suggested otherwise.

42. The board hence decided to admit the respondent's objections under Article 83 EPC to the invention as defined in claims 1, 3, 8 and 10 of auxiliary requests IXA and XIA into the appeal proceedings in accordance with Article 13(2) RPBA 2020.

Sufficiency of disclosure (Article 83 EPC)
Claims 1, 3, 8 and 10

43. The data in the patent show that the claimed methods cannot be carried out when the loading and the washing buffers have pH 8.0, i.e. a pH value that is 2.5 pH units higher than the isoelectric point of the protein VWF (see points 15., 16. and 27. above). There are no data in the patent which demonstrate that using a pH 2.6 units above the isoelectric point of VWF, i.e. a pH of 8.1, enables the removal of NLEV. In Example 1, no buffers having pH values between pH 8.0 and pH 9.0 were tested. In the sole working embodiment disclosed in the patent, the loading and the washing buffers both have pH 9.0 (see Examples 1, 3 and 4). Moreover, the patent teaches that a significant removal of NLEV is achieved when the $\log_{10}$ virus reduction factor is higher than 2 (see paragraph [0068] and point 11. above).

44. Given that the patent teaches that pH 8.0 does not work (see Example 1) and consistently performs the loading and washing steps at pH 9.0 to reliably achieve the removal of NLEVs (see Examples 1, 3 and 4), the board is not persuaded by the appellants' argument that the skilled person would find it credible that a tangible removal would be achieved when using solutions

at pH 8.1. Instead, the board agrees with the respondent that the skilled person would have had serious doubts that the claimed methods could be carried out with buffers having pH 8.1, i.e. a pH that was only 0.1 units higher than a pH value that did not work.

45. The appellants also submitted that none of the examples fell within the scope of the claims and that it was for the respondent to demonstrate that the claimed methods did not work. The board, however, agrees with the respondent that given that the patent had been revoked for lack of sufficiency of disclosure, the burden of proof is on the appellants to provide reasons why the claimed method could be carried out. The board holds that the invention as defined in claims 1, 3, 8 and 10 of auxiliary requests IXA and XIA is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art within the meaning of Article 83 EPC.

Auxiliary request XIB
Admittance (Article 13(1) RPBA 2020)

46. The set of claims of auxiliary request XIB was submitted on 18 December 2019, i.e. after the appellants had filed the statement of grounds of appeal and before notification of the summons to oral proceedings. The admission and consideration of auxiliary request XIB was therefore at the board's discretion in accordance with Article 13(1) RPBA 2020, applicable to this appeal pursuant to Articles 24 and 25 RPBA 2020. This discretion must be exercised in view of, *inter alia,* criteria on the state of the proceedings, the suitability of the amendment to resolve issues admissibly raised by another party in

the appeal proceedings or raised by the board, procedural economy and *prima facie* allowability. As the list of criteria for applying the discretion is non-exhaustive, considerations under Article 12(4) 2007, applicable in this appeal case pursuant to Article 24 and Article 25(1), (3) RPBA 2020, can likewise be taken into account when deciding on admittance.

47. Given that the claims of auxiliary request XIB had been filed prior to the entry into force of the revised version of the RPBA, the board did not apply Article 13(1) RPBA 2020 in a more restrictive manner - e.g. relating to a required reasoning - than it would have applied Article 13(1) RPBA 2007, which had been in force when the claims were filed.

48. The set of claims of auxiliary request XIB comprises the same independent claims as auxiliary request 8, i.e. the set of claims considered allowable by the opposition division. It further comprises five new claims, including four independent claims (see section VII.), by which the limitations inserted into claims 1 and 5 of auxiliary request 8 that led to the allowability of the claims were added into the then deleted claims. The inclusion of these new claims did not constitute an amendment submitted in response to any objection of the respondent. The appellants' justification for the submission of auxiliary request XIB was that the additional claims contained the same limitations inserted into claims 1 and 5 of auxiliary request 8 considered allowable by the opposition division.

49. However, when submitting the set of claims of auxiliary request 8 in the proceedings before the opposition

division, the appellants had decided not to include independent claims identical to claims 2, 3, 9 and 10 of auxiliary request XIB and had therefore prevented the opposition division from considering sufficiency of disclosure of these claims. Admitting auxiliary request XIB into the appeal proceedings would therefore require the board to consider new independent claims. This would increase the complexity of the case and go against the need for procedural economy.

50. The amendments reintroduced independent claims which had not been further pursued in opposition. Their reintroduction can also not be considered as a legitimate reaction to the decision under appeal or any objection raised by the other party. This claim set could and should have been presented in the proceedings before the opposition division. The claim set being filed together with the claims of auxiliary requests IXA and XIA which had been admitted into the proceedings by the board does not support the appellants' case since other aspects were predominant for the two other requests, in particular the consideration that these claim requests were filed in reaction to an objection of added subject-matter raised against auxiliary request VIII in appeal. While a corresponding amendment was indeed present in the claims of auxiliary request XIB, that latter request added abandoned subject-matter compared to auxiliary request 8 underlying the decision under appeal. In view of the above, the board decided not to admit auxiliary request XIB into the appeal proceedings in accordance with Article 13(1) RPBA 2020.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

A. Chavinier Tomsic M. Blasi

Decision electronically authenticated