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European Patent Office

80298 M U N I C H

EP 02 70 3958.5-1410
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP S3

München, July 25, 2016
UEX/MW/KSY

Further to our formal Notice of Appeal against the decision of March 17, 2016 to refuse the European patent application No. 02 70 3958.5 filed on May 17, 2016, we herewith provide our statement setting out the grounds of appeal in accordance with Article 108 EPC and Rule 99 EPC.

1. REQUESTS

It is requested that the decision of March 17, 2016 to refuse the European patent application No. 02 70 3958.5 be set aside and the application be granted based on the Request enclosed herewith.

As an auxiliary measure only, oral proceedings in accordance with Article 116(1) EPC are requested.

Should the Board not be able to grant the patent application based on the Request enclosed herewith, Applicant requests permission to submit further requests.

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2. NATURE OF THE AMENDMENTS (THE NEW REQUEST)

Independent claim 1 concerns a method for removing contaminant DNA in an antibody-containing sample, which comprises applying the antibody-containing sample to affinity chromatography of Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity having a molarity of 30 mM or less and a pH of 1.5 to 3.9, adjusting the pH of the resulting eluate to pH 4.3 to 7.5 by addition of a buffer and removing the resulting particles.

The new Request filed herewith corresponds to the Main Request as filed in the first instance proceedings on January 21, 2016.

However, in step 1) of claim 1, the acidic aqueous solution of low conductivity is solely defined by its molartiy of 30 mM or less and its pH of 1.5 to 3.9.

Moreover, claim 1 has been further amended to delete the feature of step 2)

> "wherein the molarity of the adjusted eluate is 30 mM or less".

These amendments are based on the disclosure on page 3, line 27 to page 4, line 7, page 5, lines 21 to 22, and page 11, lines 14 to 20 (step 1)) and page 5, lines 2 to 3 (step 2)) of the application as filed.

As none of the above amendments comprises subject-matter extending beyond the application as filed, they should be admissible within the meaning of Article 123(2) EPC.

3. ARTICLE 123(2) EPC

In view of the amended claims constituting the Request, the objections raised under items 1.1.1 with regard to step 1) and 1.1.2 with regard to step 2) of claim 1 should be rendered moot.

Thus, the new Request should meet the requirements of Article 123(2) EPC.

4. ARTICLE 84 EPC

We submit that it is clear for a mind willing to understand that an acidic aqueous solution of low conductivity cannot not have molarity of zero and that thus such a solution is not covered by the claim.

As agreed by the Examining Division under item 1.2.1, the nature of the acidic solution in step 1) should be clear.

Furthermore, we submit that it is also clear to a person of skill in the art that the acid compound, e.g., citric acid, hydrochloric acid or acetic acid, should have a molarity of 30 mM or less in the acidic aqueous solution of low conductivity of claim 1, step 1).

In view of the above explanations and the fact that the claims of the new Request no longer cite the objected to terms "ionic strength" and "low conductivity" and the step 2) has been amended as discussed above, the claims of the new Request should meet the requirements of Article 84 EPC.

5. ARTICLES 54 AND 56 EPC

We submit that the subject-matter of the new Request on file is novel and inventive over the cited prior art documents. Full reference is made to our submissions made in the first instance.

Dr. Alexa von Uexküll
European Patent Attorney

Encl.:
New Request (marked-up and clean copy)

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Application No.	Ref.	Date
02 703 958.5 - 1410	H 2624 EP S3	17.03.2016
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA		

Decision to refuse a European Patent application

The Examining Division - at the oral proceedings dated 23.02.2016 - has decided:

European Patent application No. 02 703 958.5 is refused.

Applicant/s:
CHUGAI SEIYAKU KABUSHIKI KAISHA
5-1, Ukima 5-chome,
Kita-ku
Tokyo, 115-8543
JP

Title
PROTEIN PURIFICATION METHOD

The grounds for the decision are set out on the supplemental sheets annexed hereto.

Means of redress

This decision is open to appeal.
Attention is drawn to the attached text of Articles 106 to 108 EPC and Rules 97 and 98 EPC.

Examining Division:

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2nd Examiner:	Bonello, Steve
1st Examiner:	Sommer, Birgit

Bertoni, Sara
Formalities Officer
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Enclosure(s): 7 page/s reasons (Form 2916)
Form 2019
MR, AR1, AR2 of 21.02.2016

to EPO postal service: 14.03.16

Summary of Facts and Submissions

1 European patent application No. 02 703 958.5 having the title "PROTEIN PURIFICATION METHOD" was filed on 11.03.2002. It claims priority of JP 2001067111 filed on 09.03.2001 and was published as WO 02/072615 on 19.09.2002. The applicant is CHUGAI SEIYAKU KABUSHIKI KAISHA, JP.

2 On entry into the regional phase before the EPO, the applicant filed an amended set of claims 1-22. With letter of 28.02.2006, the examining division raised objections under **Articles 123(2), 82, 83/84** and **84 EPC**.

3 The applicant provided argumentation and an amended set of claims with letter of 04.09.2006. The applicant requested oral proceedings according to **Article 116(1) EPC** in case of an unfavourable decision. The examining division provided a detailed response on 09.08.2007 and raised or maintained objections under **Articles 54, 56, 82, 83/84** and **84 EPC**.

4 With letter of 04.12.2007, the applicant provided further argumentation and an amended set of claims. Third party observations were filed on 04.04.2008 attacking those claims under **Article 54 EPC**. The examining division provided a detailed response on 23.10.2009 and raised or maintained objections under **Articles 54, 56, 83/84, 84** and **123(2) EPC**.

5 The applicant provided argumentation and amended sets of claims with letters of 19.04.2010, 28.09.2011, 22.11.2012 and 30.07.2013, respectively. The examining division raised or maintained objections under **Articles 54, 56, 82, 83/84, 84** and/or **123 (2) EPC** with communications of 30.03.2011, 16.05.2012 and 24.01.2013, respectively.

6 On 03.06.2015, the examining division summoned the applicant to oral proceedings according to **Rule 115 EPC** to be held on 08.10.2015 in order to discuss outstanding objections under **Articles 54, 56, 83/84, 84** and **123(2) EPC** which were outlined in the communication accompanying the summons.

7 The applicant responded to the summons with letter of 03.09.2015 and submitted a Main Request as well as Auxiliary Requests 1 and 2. The examining division informed the applicant with communication of 24.09.2015 that objections under **Articles 83/84, 84** and **123(2) EPC** are maintained.

8 Third party observations were filed on 02.10.2015 attacking the Main Request as well as Auxiliary Requests 1 and 2 under **Articles 54, 84** and **123(2) EPC**. The applicant submitted Auxiliary Requests 3 and 4 with letter of 06.10.2015. In view of the *prima facie* relevant third party observations, the oral proceedings on 08.10.2015 were postponed by the examining division.

9 On 12.10.2015, the examining division summoned the applicant to oral proceedings according to **Rule 115 EPC** to be held on 23.02.2016 in order to discuss outstanding objections under **Articles 54, 56, 83/84, 84** and **123(2) EPC** which were outlined in the communication accompanying the summons.

10 The applicant responded to the summons with letter of 21.01.2016 and submitted a new Main Request as well as Auxiliary Requests 1 and 2. The examining division informed the applicant with communication of 25.02.2016 (faxed in advance on 18.02.2016) that objections under **Articles 56, 83/84, 84** and **123(2) EPC** are maintained against all requests on file.

11 Oral proceedings were held on 23.02.2016. At the end, the examining division decided to refuse the application.

Reasons for the Decision

The decision is based on the following request(s):

Main Request

Description, Pages

1-17, 19-24, 26	filed with entry into the regional phase before the EPO			
18, 25	received on	27-10-2003	with letter of	24.10.2003

Claims, Numbers

1-11	received on	21-01-2016	with letter of	21-01-2016

Auxiliary Request 1

Description, Pages

1-17, 19-24, 26	filed with entry into the regional phase before the EPO			
18, 25	received on	27-10-2003	with letter of	24.10.2003

Claims, Numbers

1-10	received on	21-01-2016	with letter of	21-01-2016

Auxiliary Request 2

Description, Pages

1-17, 19-24, 26	filed with entry into the regional phase before the EPO			
18, 25	received on	27-10-2003	with letter of	24.10.2003

Claims, Numbers

1-9	received on	21-01-2016	with letter of	21-01-2016

The claims under consideration are attached to this decision. As to the other application documents, reference is made to the file.

1 **Main Request:**

Independent claim 1 concerns a method for removing contaminant DNA in an antibody-containing sample, which comprises applying the antibody-containing sample to affinity chromatography on Protein a or Protein G to elute the antibody with an acidic aqueous solution of low conductivity as specified in the claim, adjusting the pH of the resulting eluate to pH 4.3 to 7.5 by addition of a buffer and removing the resulting particles.

Independent claim 11 relates to a method for manufacturing a purified antibody, which comprises the steps of the method according to claim 1.

1.1 Amendments (**Article 123 EPC**)

1.1.1 No basis can be found in the application as originally filed for the combination of features defining the acidic aqueous solution in claim 1, step 1). According thereto, the antibody it eluted either with a) "*... an acidic aqueous solution of low conductivity of a ionic strength of 0.2 or less [...] and having a molarity of 30mM or less*" or with b) "*... an acidic aqueous solution of [....] a conductivity of 300 mS/m or less and having a molarity of 30 mM or less*".

The applicant cited original claims 1, 3- 6 and 8 as well as pages 11, lines 12-19 of the description as alleged basis. The applicant further argued that ionic strength, conductivity and molarity are to be seen as equivalent alternatives for defining the same acidic aqueous solution. Therefore, a skilled person would understand that those parameters can be used in combination.

This argumentation cannot be followed. None of the cited passages discloses the combination of a specific molarity with either a specific ionic strength or a specific conductivity for defining the elution buffer. The acidic aqueous solution of low conductivity is rather defined e.g. on page 11, lines 12-20, of the description as "*... an aqueous solution of pH 1.5 to pH 3.9 [...] which has a molarity of [...] 0 to 30 mM [...] or has a ionic strength of 0 to 0.2 [...] or has a conductivity of 0 to 300 mS/m [...]*".

Even if the values selected in claim 1.1) for ionic strength (*"...0.2 or less..."*), conductivity ("*... 300 mS/m or less...*") or molarity ("*... 30 mM or less...*") are present as possible alternatives in said passage of the description, the combination of those ranges for defining an elution buffer is not disclosed.

A specific combination - unsupported by the application as filed - of one item from different lists of features means that although the application as filed might conceptually comprise the claimed subject-matter, it does not however disclose it in that particular individual form (**T0602/05,** point 7. of the reasons).

Moreover, it is not apparent for a skilled person from the application as originally filed that the specific selections for ionic strength, conductivity and molarity will necessarily define in the same acidic aqueous solution of low conductivity and thus can be used in (redundant) combination. It is noted that in claim 1 of the Main Request the broadest possible range for ionic strength (*"...0.2 or less..."*) and conductivity ("*... 300 mS/m or less...*"), respectively, is combined with the smallest possible range for molarity ("*... 30 mM or less...*") as disclosed e.g. on page 11, lines 12-20. Such a combination is not immediately apparent for a skilled person from the original application.

In contrast, a skilled person reading e.g. page 11, lines 12-20 of the description as originally filed, would interpret the three parameters ionic strength, conductivity and molarity immediately as three different ways of defining an elution buffer which are independent from each other.

1.1.2 No basis can be found in the original application for the feature "...*wherein the molarity of the adjusted sample/eluate is 0 to 30 mM..*" in claim 1.2).

The applicant cited original claims 1 and 4- 6 as well as page 10, lines 5-12 of the description as alleged basis. The applicant further argued that the use of a neutral solution is to be seen as common concept which is present in any of the claims as originally filed. Therefore, the definition of the neutral solution on page 10, lines 5-12 also applies to claim 1 of the Main Request.

This argumentation cannot be followed. The molarity neither of the acid nor of any other compound in the eluate is derivable from any part of the description. It is not even possible to vaguely estimate the molarity of the acid in the eluate, since the examples are silent with respect to the volumes of equilibration buffer, washing buffer and elution buffer. Any statement about the molarity of the eluate is mere speculation.

Moreover, original claim 1 as well as the passage on page 10 refer to a method which was not found unitary with the method in claim 1 of the Main Request (based on claim 3 as originally filed). It is not allowable to construct a basis for a claim by artificially combining passages which are taken from different parts of the description if said passages were not mentioned in the same context in the application as originally filed. The Boards of Appeal decided that "*...in accordance with the case law (e.g. **T349/01** of 28 January 2004 and **T157/90** of 12 September 1991), it is not permissible under **Article 123(2) EPC**, to claim subject-matter which combines elements scattered throughout the application as filed unless it would be totally clear and unambiguous that they were meant to be combined.*" (**T0001/08,** reasons of the decision, item 12).

1.2 Clarity (**Article 84 EPC**)

1.2.1 The nature of the acidic aqueous solution in claim 1.1) is open to interpretation. It is unclear, how a solution with e.g. a molarity of 0 mM, i.e. without any ionic compound, can have a pH of 1.5 to 3.9.

The applicant argued that It is clear for a mind willing to understand that an acidic aqueous solution of low conductivity cannot not have a ionic strength, conductivity or molarity of zero. Such a solution is not covered by the claim.

This argumentation can be followed.

1.2.2 The definition of the parameter "*conductivity*" in claim 1.1) is unclear, since said parameter depends on several factors, e.g. the temperature. It is not clarified in the specification at what temperature the conductivity must be measured to determine whether the claim requirements are met.

The applicant argued that a person skilled in the art is aware that the conductivity is usually to be determined at ambient conditions unless indicated otherwise.

This argumentation can be followed.

1.2.3 It is unclear to which compound(s) the parameter "*... molarity of 30 mM or less...* " in claim 1.1) and 1.2) refers to.

The applicant argued that a skilled person would clearly understand which acidic solutions are applicable to the claimed method.

This argumentation cannot be followed.

A skilled person might assume, that the acid compound, e.g. citric acid, hydrochloric acid or acetic acid, should have a molarity of 30 mM or less in the acidic aqueous solution of low conductivity of claim 1.1). It appears, however, from applicant's letter of 22.11.2012 that said term should be interpreted differently at least in claim 1.2), i.e. as combined molarity of all compounds present in the pH-adjusted acidic aqueous solution (applicant's letter of 22.11.2012, e.g. page 2, last sentence of third paragraph; page 2-3, item 2., discussion of D3). It is therefore open to interpretation to which compounds the parameter molarity refers to in claim 1.

In any case, the application does not technically support the assessment of molarity of an eluate.

1.2.4 The definition of the parameter "*ionic strength*" is unclear, since it is not indicated which unit has to be used for said parameter.

The applicant argued that it is clearly understood by a skilled person that the unit of ionic strength is mM in view of the unit of molarity (description, page 11, lines 12-20).

This argumentation cannot be followed.

Claim 1.1) only discloses that the solution should have "*...an ionic strength of 0.2 or less...*" without giving any unit. Even if it is known that ionic strength is typically presented in units of molality or molarity, the value "*...0.2 or less...*" could refer to e.g. 0.2 µM, 0.2 mM or 0.2 M.

Moreover, the passage in the description, page 11, lines 12-20, clearly states that the acidic aqueous solution of low conductivity can be defined either by its molarity or by its ionic strength or by its conductivity. The unit of the ionic strength is therefore not dictated by a specific molarity.

1.3 In conclusion, the examining division is of the opinion that the Main Request does not meet the requirements of **Articles 123** and **84 EPC**.

2 **Auxiliary requests 1 and 2:**

The argumentation outlined above applies *mutatis mutandis* to claim 1 of Auxiliary Request 1 and 2. Both Auxiliary Requests also contain the passages mentioned above which are objected to as lacking clarity and comprising unallowable amendments.

Therefore, none of the two requests meets the requirements of **Articles 123** and **84 EPC**.

Decision

In accordance with **Article 97(2) EPC**, the application, which fails to meet the requirements of **Articles 84** and **123(2) EPC** is refused in its entirety.

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By fax in advance
Fax: 0049 89 413 04 111

Date
25.02.2016

Reference	Application No./Patent No.
H 2624 EP S3	02703958.5 - 1410 / 1380589

Applicant/Proprietor
CHUGAI SEIYAKU KABUSHIKI KAISHA

BRIEF COMMUNICATION

Oral Proceedings on 23.02.16

Subject: ☒ Your letter of 21.01.2016

Communication:

☐ The summons to attend oral proceedings on 23.02.16 has been cancelled.

☐ The procedure will be continued in writing.

☒ The date fixed for oral proceedings is maintained.

☐ A new date will be set later.

☒ Please see attached Form 2906.
Please confirm receipt of this communication.

Please take note.

For the Examining Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Registered letter

The examination is being carried out on the **following application documents**

Main Request

Description, Pages

1-17, 19-24, 26	filed with entry into the regional phase before the EPO			
18, 25	received on	27-10-2003	with letter of	24.10.2003

Claims, Numbers

1-11	received on	21-01-2016	with letter of	21-01-2016

Auxiliary Request 1

Description, Pages

1-17, 19-24, 26	filed with entry into the regional phase before the EPO			
18, 25	received on	27-10-2003	with letter of	24.10.2003

Claims, Numbers

1-10	received on	21-01-2016	with letter of	21-01-2016

Auxiliary Request 2

Description, Pages

1-17, 19-24, 26	filed with entry into the regional phase before the EPO			
18, 25	received on	27-10-2003	with letter of	24.10.2003

Claims, Numbers

1-9	received on	21-01-2016	with letter of	21-01-2016

Main Request:

1 Amendments (**Article 123(2) EPC**)

1.1 The objections raised in the communication accompanying the summons to oral proceedings of 12.10.2015 are **maintained in its entirety** for the reasons already outlined in detail in the previous communications of 12.10.2015, 24.09.2015, 03.06.2015, 24.01.2013, 16.05.2012 and 30.03.2011. The proposed amendments actually neither address nor overcome said objections.

1.2 With letter of 21.01.2016, the applicant merely reiterated the argumentation filed with letters of 22.11.2012, 31.07.2013 and 03.09.2015. Said argumentation is still not convincing and was countered in detail in the previous communications.

2 Novelty (**Article 54 EPC**)

The argumentation of the applicant filed with letter of 21.01.2016 can be followed. Reference to a molarity of 30 mM or less in claim 1 renders the claims novel over D3.

3 Inventive step (**Article 56 EPC**)

3.1 The objection that the technical problem has not been solved over the whole claimed scope is **maintained in its entirety** for the reasons already outlined in detail in the previous communications.

Briefly, the Examining Division has serious doubts, that all methods falling under the scope of the claims actually remove contaminant DNA from an antibody-containing sample. Negative examples are already given in the description.

3.2 The applicant argued with letter of 21.01.2016 that examples were the pH of the eluate is adjusted to pH 4.0 are no longer covered by the present claims.

3.3 This argumentation can be followed in principle.

However, there are further examples in the description which raise doubts that the methods can be put into practice over their whole claimed scope.

For example, page 23, tables 5 and 6 disclose the residual amount of DNA in filtered eluates which where adjusted to pH levels between 4.5 and 7.5. In experiment 2 (table 6) the amount of DNA in the unfiltered sample (4330 pg/ml) was reduced to levels between 34-164 pg/ml, depending on the selected pH and time period. In contrast, samples at pH7.5 still show 1142 or 3288 pg/ml residual DNA (experiment 1, table 5). It is unclear, if and to what extend the DNA was removed at pH7.5, since experiment 1 does not disclose the amount of DNA contamination in the unfiltered sample but only the DNA contamination in the culture medium. Assuming that the Protein A affinity chromatography in experiment 1 has a DNA reducing effect which is

comparable to the effect observed in experiment 2 (i.e. reducing the DNA contamination in the range of three orders of magnitude from 5448000 pg/ml to 4330 pg/ml) , the DNA contamination in the unfiltered sample of experiment 1 is extrapolated to approx. 235 pg/ml. Then, however, a removal of residual DNA by adjusting the pH of the eluate can be observed neither at pH 7.5 nor at pH 6.5 (table 5). Such negative examples fall under the scope of the claims but they do not solve the technical problem. Consequently, such methods cannot be considered as being inventive.

Moreover, the application does not contain any example disclosing the conductivity or ionic strength of the elution solution, let alone the molarity of the adjusted eluate. Speculating about the effect of a method without providing any credible experimental proof for its ability to remove contaminant DNA is not a task that justifies the acknowledgement of an inventive step. The objection is **maintained in its entirety** that the present claims are merely hypothetical and represent an invitation to start a research project. At present, it is not credible, that the problem actually has been solved.

Since the problem has not been credibly solved over the whole scope, claims 1-11 do not meet the requirements of **Article 56 EPC**.

4 Sufficiency of disclosure and support in the description (**Articles 83/84 EPC**)

4.1 The objections **are maintained in its entirety** for the reasons already outlined in the previous communications. The broad scope of the current claims is not justified by the technical contribution of the present application.

Briefly, the application only provides adequate guidance to remove contaminant DNA in an antibody-containing sample by applying the sample to affinity chromatography on Protein A, eluting the antibody using 20 mM citric acid buffer, pH 2.7, adjusting the pH to specific values and removing the resulting particles (examples 2 and 3). Examples 1-3 are silent with respect to conductivity or ionic strength of the elution solution let alone the molarity of the adjusted eluate. Since the claimed methods have not been shown in the application, it would require undue burden to put the invention into practice. Moreover, the ionic strength of the acidic aqueous solution is not defined in a specific unit and it is unclear at which temperature the conductivity of the acidic aqueous solution must be measured. It is further not evident how such a solution could possibly have an ionic strength or a conductivity of zero.

4.2 The applicant argued with letter of 21.01.2016 that the teaching of the examples can be extrapolated to Protein G affinity chromatography, that citric acid is one example of an acidic aqueous solution as claimed and that a

skilled person will understand the unit of ionic strength and the condition for determining conductivity based on the description and his technical knowledge.

4.3 This argumentation cannot be followed. The application fails to provide even a single reproducible example of the specific method as claimed including all its features. Moreover, the skilled person has to make several assumptions or selections for defining parameters of the method, e.g. for defining the ionic strength or the conductivity of the elution solution.

5 Clarity (**Article 84 EPC**)

5.1 The objections are **maintained in its entirety** for the reasons outlined in the previous communication.

Briefly, the nature of the acidic aqueous solution to be used in claim 1.1) is open to interpretation and it is not clear to which compound(s) the parameter "*... molarity of 30 mM or less...* " in claim 1.1) and 1.2) refers to. Furthermore, the definition of the parameters "*ionic strength*" and "*conductivity*" in claim 1.1) is unclear

5.2 The applicant argued with letter of 21.01.2016 that a skilled person would clearly understand which acidic solutions are applicable to the claimed method. Moreover, it is clearly understood by a skilled person that the unit of ionic strength is mM in view of the unit of molarity (description, page 11, lines 12-20. Unless indicated otherwise, the conductivity is to be determined at ambient conditions.

5.3 This argumentation cannot be followed. It is e.g. unclear, how a solution with e.g. an overall molarity of 0 mM, i.e. without any ionic compound, can have a pH of1.5 to 3.9 as required by claim 1.1). Moreover, the passage in the description clearly states that the acidic aqueous solution of low conductivity can be defined either by its molarity or by its ionic strength or by its conductivity. Therefore, the unit of the ionic strength is not dictated by a specific molarity and thus unclear.

Finally, an additional objection as to lack of clarity is raised against claim 3 which attempts to define the subject-matter in terms of the result to be achieved. Such a definition is not allowable because it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved.

Auxiliary requests 1 and 2:

6 The argumentation outlined above applies *mutatis mutandis*. None of those requests meets the requirements of **Articles 123, 56, 83 and 84 EPC**.

7 Since none of the requests on file overcomes the objections raised above, the summons to oral proceedings are maintained. During the oral proceedings the above mentioned objections will be discussed.

A refusal of the application under **Article 97(2) EPC**, in particular due to failure to overcome objections under **Article 123, 56** and **83/84 EPC**, has to be expected.

In view of the 14 sets of amended claims filed during examination, the applicant had sufficient opportunity to file a set of claims overcoming the objections by the Examining Division.

Therefore, the applicant will be allowed to file **only one single additional set of amended claims** during oral proceedings and **only if said amendments are suitable to overcome the objections made above and do not create additional objections** (**Rule 137(3) EPC**).

The attention of the applicant is drawn to the possibility to request a decision "according to the state of the file" (**Guidelines, E-X, 4.4**).

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21 Jan. 2013

EP 02 70 3958.5
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP S3

NEW AUXILIARY REQUEST 1

1. A method for removing contaminant DNA in an antibody-containing sample, which comprises the following steps:
   1) applying the antibody-containing sample to affinity chromatography on Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity of an ionic strength of 0.2 or less or a conductivity of 300 mS/m or less and having a molarity of 30 mM or less, wherein the acidic aqueous solution has a pH of 1.5 to 3.9 and wherein the acidic aqueous solution is selected from aqueous solutions of hydrochloric acid, citric acid and acetic acid;
   2) adjusting the pH of the resulting eluate to pH 4.3 to 7.5 by addition of a buffer, wherein the molarity of the adjusted eluate is 30 mM or less; and
   3) removing the resulting particles.

2. The method according to claim 1, wherein the contaminant DNA is present at a DNA concentration of 22.5 pg/ml or less in the treated sample containing an antibody.

3. The method according to claim 1, wherein the buffer is an aqueous solution of Tris.

4. The method according to claim 1, wherein the antibody is a humanized monoclonal antibody.

5. The method according to claim 4, wherein the antibody is a humanized anti-IL-6 receptor antibody.

6. The method according to claim 4, wherein the antibody is a humanized anti-HM1.24 antigen monoclonal antibody.

7. The method according to claim 4, wherein the antibody is a humanized anti-parathyroid hormone-related peptide antibody (anti-PTHrP antibody).

8. The method according to claim 4, wherein the antibody is a humanized anti-tissue factor antibody.

9. The method according to claim 1, wherein the particles are removed by filtration through a filter.

10. A method for manufacturing a purified antibody, which comprises the steps of the method according to claim 1.

EP 02 70 3958.5
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP S3

NEW MAIN REQUEST

1. A method for removing contaminant DNA in an antibody-containing sample, which comprises the following steps:
   1) applying the antibody-containing sample to affinity chromatography on Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity of an ionic strength of 0.2 or less or a conductivity of 300 mS/m or less and having a molarity of 30 mM or less, wherein the acidic aqueous solution has a pH of 1.5 to 3.9;
   2) adjusting the pH of the resulting eluate to pH 4.3 to 7.5 by addition of a buffer, wherein the molarity of the adjusted eluate is 30 mM or less; and
   3) removing the resulting particles.

2. The method according to claim 1, wherein the acidic aqueous solution is selected from aqueous solutions of hydrochloric acid, citric acid and acetic acid.

3. The method according to any one of claims 1 or 2, wherein the contaminant DNA is present at a DNA concentration of 22.5 pg/ml or less in the treated sample containing an antibody.

4. The method according to claim 1, wherein the buffer is an aqueous solution of Tris.

5. The method according to claim 1, wherein the antibody is a humanized monoclonal antibody.

6. The method according to claim 5, wherein the antibody is a humanized anti-IL-6 receptor antibody.

7. The method according to claim 5, wherein the antibody is a humanized anti-HM1.24 antigen monoclonal antibody.

8. The method according to claim 5, wherein the antibody is a humanized anti-parathyroid hormone-related peptide antibody (anti-PTHrP antibody).

9. The method according to claim 5, wherein the antibody is a humanized anti-tissue factor antibody.

10. The method according to claim 1, wherein the particles are removed by filtration through a filter.

11. A method for manufacturing a purified antibody, which comprises the steps of the method according to claim 1.

EP 02 70 3958.5
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP S3

NEW AUXILIARY REQUEST 2

1. A method for removing contaminant DNA in an antibody-containing sample, which comprises the following steps:
   1) applying the antibody-containing sample to affinity chromatography on Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity of an ionic strength of 0.2 or less and a conductivity of 300 mS/m or less and having a molarity of 30 mM or less, wherein the acidic aqueous solution has a pH of 1.5 to 3.9;
   2) adjusting the pH of the resulting eluate to pH 4.3 to 7.5 by addition of a buffer, wherein the molarity of the adjusted eluate is 30 mM or less; and
   3) removing the resulting particles by filtration through a filter,

   wherein the acidic aqueous solution is selected from aqueous solutions of hydrochloric acid, citric acid and acetic acid.

2. The method according to claim 1, wherein the contaminant DNA is present at a DNA concentration of 22.5 pg/ml or less in the treated sample containing an antibody.

3. The method according to claim 1, wherein the buffer is an aqueous solution of Tris.

4. The method according to claim 1, wherein the antibody is a humanized monoclonal antibody.

5. The method according to claim 4, wherein the antibody is a humanized anti-IL-6 receptor antibody.

6. The method according to claim 4, wherein the antibody is a humanized anti-HM1.24 antigen monoclonal antibody.

7. The method according to claim 4, wherein the antibody is a humanized anti-parathyroid hormone-related peptide antibody (anti-PTHrP antibody).

8. The method according to claim 4, wherein the antibody is a humanized anti-tissue factor antibody.

9. A method for manufacturing a purified antibody, which comprises the steps of the method according to claim 1.

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European Patent Office

80298 M U N I C H

EP 02 70 3958.5-1410
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP S3

München, January 21, 2016
UEX/MW/KSY

This is in response to the summons to attend oral proceedings dated October 12, 2015.

In preparation of the oral proceedings scheduled for February 23, 2016, we herewith submit a new Main Request and new Auxiliary Requests 1 and 2, which should form the basis of the further prosecution of the application.

1. NATURE OF THE AMENDMENTS

1.1 New Main Request

The new Main Request corresponds to the Main Request as filed on September 3, 2015. Moreover, the molarity of the aqueous solution in step 1 and the acidic molarity of the adjusted eluate in step 2 has been amended to "30 mM or less".

This amendment is based on the disclosure on page 10, line 9, and page 11, line 17, respectively.

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1.2 New Auxiliary Request 1

Auxiliary Request 1 corresponds in essence to the new Main Request. However, the acidic aqueous solution in step 1 of claim 1 has been more closely defined by introducing the feature of previous claim 2.

This amendment is based, inter alia, on the disclosure on page 4, lines 14 to 20 and claims 7 to 8 as originally filed.

Previous claim 2 has been deleted, the remaining claims have been renumbered and the dependencies amended accordingly.

1.3 New Auxiliary Request 2

The new Auxiliary Request 2 corresponds to the Auxiliary Request 3 as filed on October 6, 2015. Furthermore, the aqueous acidic solution in step 1 of claim 1 and the molarity in steps 1 and 2 has been defined as discussed for new Auxiliary Request 1, above.

Previous claim 2 has been deleted, the claims have been renumbered and the dependencies amended accordingly.

As none of the above amendments comprises subject-matter extending beyond the application as filed, the new Main Request and new Auxiliary Requests 1 and 2 should be allowable within the meaning of Article 123(2) EPC.

2. MAIN REQUEST

2.1 Article 123(2) EPC

The claims previously on file have been objected to as contravening the requirements of of Article 123(2) EPC.

Applicant disagrees and maintains that the feature also in its amended form "30 mM or less" finds a clear and unambiguous basis in the specification as filed, particularly on pages 10 to 12, and in original claim 1.
As can be seen from original claim 1 and the disclosure on page 10, lines 1 to 2, the conversion of the sample into a neutral aqueous solution of low conductivity is an

essential feature of the method according to the present invention. Specific embodiments of the method are described on pages 10 to 12 of the specification.
From the description on pages 10 to 12, it can be clearly understood that the adjusted eluate in present claim 1 corresponds to "a neutral aqueous solution of low conductivity". Lines 5 to 8 of page 10 clearly define that "a neutral aqueous solution of low conductivity" has a pH of 4 to 8 and a molarity of 0 to 100 mM, and more preferably 0 to 30 mM (i.e. 30 mM or less).

It is, moreover, self-speaking for a person of skill in the art to derive that if a sample containing a physiologically active protein is converted into a solution of low conductivity by affinity chromatography with a solution of low conductivity, any adjustment of the pH of the resulting solution needs also to be carried out in a way such as to maintain the low conductivity of the eluate.

Furthermore, the Examiner has objected to the combination of a specific molarity with a specific ionic strength or conductivity in step 1 of claim 1.

Step 1 of claim 1 finds basis in claim 3 as filed in combination with original claims 4, 5, 6, and 8 and the disclosure of page 11, lines 10 to 20.

Thus, the subject-matter of the new Main Request clearly conforms with the requirements of Article 123(2) EPC.

2.2 Novelty over D3

According to the Examiner, the method of claim 1 lacks novelty over D3 (WO 95/22389), inter alia referring to third party observations filed on October 2, 2015. Applicant submits that D3 does not disclose the feature of "a molarity of 30 mM or less" of claim 1, as amended.

On pages 2 and 3 of the observations, the third party refers to Example IA of D3.

However, as will be demonstrated in detail below, the subject-matter of the Main Request is novel over D3.

Example IA in D3 (in particular, page 19, lines 9 to 19) discloses:

- the IgG was eluted by applying 15-20 l of ProSep A elution buffer (25 mM citrate, pH 3.5, see Table 1 on page 18 of D3);
- immediately after elution, the sample was adjusted to pH 3.5 by the addition of 2.5 M HCl, held for approximately 30 minutes, and adjusted to pH 5.5 by the addition of approximately 350 ml of 1 M Tris base;

- thereafter, the sample was filtered through a 0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200, into a sterile container.

Thus, the eluent before the filtration has:
- 375 mmol (25 mM • 15 l) of citrate
- "x" mmol (2.5 M • "Y" l (unknown)) of HCl
- 350 mmol (1 M • 0.35 l) of Tris base
- at least 15.35 l (15 l + "Y" l +0.35 l) in total volume.

Based thereon, the molarity of the eluent can be calculated to at least:
(375 + 350)/15.35 = 47.2 mM.

Thus, the subject-matter of the new Main Request requiring a molarity of the eluate of 30 mM or less is novel over D3.

2.3 Inventive step

As an introductory note, it is submitted that D3 does not disclose or suggest to adjust the molarity of the eluate to 30 mM or less, which is the essential feature distinguishing the present invention over D3.

According to the Examining Division, the problem has not been solved over the whole scope of the claims, as adjusting the pH of the eluate to, e.g., pH 4.0 does not result in removal of the contaminating DNA.

Full reference is made to our previous submissions dated September 3, 2015 under item 3. As claim 1 has been amended to state that the eluate obtained from step 1 is adjusted to pH 4.3 to 7.5 and to a molarity of 30 mM or less, it thus does not encompass non-working embodiments.

The arguments laid out in detail for the previous Main Request filed on September 3, 2015 apply, *mutatis mutandis*, for the new Main Request.

2.4 Sufficiency of disclosure and support in the description (Articles 83/84 EPC)

According to the Examining Division, the subject-matter of the present application does not meet the requirements of Articles 83/84 EPC, as the application only provides adequate guidance in Examples 2 and 3 to remove contaminant DNA in an antibody containing sample by applying the sample to affinity chromatography on Protein A.

Protein A and Protein G share the common property of binding the Fc region of an antibody, and therefore, if a method using Protein A is specifically and detailed disclosed in the application, a person skilled in the art will be in the position to carry out a method using Protein G without undue experimentation using his technical general knowledge.

Further, the description specifically discloses antibody purification using aqueous citric acid in Examples 2 and 3. Citric acid is an acid aqueous solution that satisfies the parameter defined in the description (page 11, lines 12 to 22). Thus, a person skilled in the art would understand that the acid aqueous solution as claimed can be used in a method for removing DNA from a sample containing antibody.

Thus, a person skilled in the art is clearly in the position to carry out the present invention as a whole without undue experimentation based on the disclosure in the present application using his technical general knowledge.

Furthermore, with regard to the objection that the unit of ionic strength is not defined by the specification, and that a condition for determining "conductivity" is not defined. As explained in detailed in item 2.5, below, a person skilled in the art will understand the unit of ionic strength and the condition for determining conductivity, based on the description and his technical common knowledge.

Thus, the new Main Request meets the requirements of Articles 83/84 EPC.

2.5 Clarity (Article 84 EPC)

It is asserted that the term "acidic aqueous solution" in step 1 of claim 1 is unclear. The scope of the term is commonly used among persons skilled in the art (to whom the teaching of an application is directed), and thus a person skilled in the art would recognize which acidic solutions fall under the parameters as defined in claim 1.

Loading a sample containing an antibody in a neutral buffer (loading buffer) on a Protein A column or Protein G column followed by eluting the antibody retained in the column by an acidic aqueous solution is a familiar step for a person skilled in the art. Thus, a person skilled in the art would clearly understand which acidic aqueous solutions are applicable to the claimed method. In this context, it is also noted that the solutions have been more closely defined by introducing the feature of previous claim 2.

It has, moreover, been asserted that the terms "ionic strength" and "conductivity" are unclear. It is noted that the present specification discloses on page 11, lines 12 to 20:

> " "acidic aqueous solution of low conductivity" generally refers to an aqueous solution of pH 1.5 to pH 3.9, preferably of pH 2.0 to pH 3.9, more preferably of pH 2.0 to pH 3.0, which has a molarity of 0 to 100 mM, preferably 0 to 50 mM, more preferably 0 to 30 mM, or has an ionic strength of 0 to 0.2, preferably 0 to 0.12, or has a conductivity of 0 to 300 mS/m, preferably 0 to 200 mS/m, more preferably 0 to 150 mS/m."

From said disclosure, it is clear for a person skilled in the art that low conductivity of an acidic solution refers to an aqueous solution of pH 1.5 to 3.9 with a specific molarity of 0 to 100 mM; or with an ionic strength of 0 to 0.2; or with a conductivity of 0 to 30 mS/m. Further, it is clearly understood that the unit of ionic strength is mM in view of unit of molarity; and that conductivity is determined under ambient conditions if no further conditions are disclosed.

Thus, the claims of the new Main Request meet the requirements of Article 84 EPC.

3. NEW AUXILIARY REQUESTS 1 AND 2

3.1 Article 123(2) EPC

In addition to the arguments for the new Main Request under item 2.1, above, it is submitted that claim 7 as filed clearly discloses the combination of conductivity, ionic strength, pH and the specific acidic aqueous solutions.

3.2 The arguments under items 2.2 to 2.4, above, apply, *mutatis mutandis*, to new Auxiliary Requests 1 and 2.

4. REQUESTS

With the above explanations and amendments to the Main Request or any of the Auxiliary Requests, Applicant has satisfied all requirements set forth in the Communication accompanying the summons.

There should thus be no need for oral proceedings. We request written confirmation in this regard.

If, however, the Examining Division does not agree with the above, it is requested that a further Communication pursuant to Article 94(3) EPC and Rule 71(2) EPC be issued. If

deemed expedient, an informal interview is requested. The undersigned is prepared to discuss minor amendments over the phone.

Dr. Alexa von Uexküll
European Patent Attorney

Encl.:
Main Request (marked-up and clean copy)
Auxiliary Requests 1 and 2 (marked-up and clean copies)

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Questions about this communication ?
Contact Customer Services at www.epo.org/contact

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ALLEMAGNE

Date
12-10-2015

Reference	Application No./Patent No.
H 2624 EP S3	02703958.5 - 1410 / 1380589
Applicant/Proprietor	
CHUGAI SEIYAKU KABUSHIKI KAISHA	

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent application.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will not be public, will take place before the Examining Division

on 23.02.16 at 09.00 hrs at the EPO,
PschorrHöfe, Bayerstr. 34, 80335 Munich

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 1/2009, 68). If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC, see also OJ EPO 10/2008, 471).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the Special edition No. 3 OJ EPO 2007, L.1., concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC) is 22.01.16.

The actual room number as well as the waiting room numbers will be given to you by the porter in the foyer at the above EPO address.

Parking is available in the underground car park, accessible only via the entrance "Grasserstrasse 2/6". On presentation of the summons to oral proceedings at one of the porters' lodges in the PschorrHöfe, the parking ticket will be revoked.

1st Examiner:	2nd Examiner:	Chairman:
Sommer B	Bonello S	Stoyanov B

For the Examining Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Annexes:
Confirmation of receipt (Form 2936)
Communication (EPO Form 2906)

Registered letter with advice of delivery to EPO postal service: 06.10.15

Confirmation Copy

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Patentanwälte Rechtsanwälte mbB

Via Telefax - 9 page(s)
Fax-No. 089-2399-4465

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EPO - Munich
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06. Okt. 2015

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EP 02 70 3958.5-1410
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP S3

München, October 6, 2015
UEX/KSY

VERY URGENT!
ORAL PROCEEDINGS ON OCTOBER 8, 2015!

In preparation of the oral proceedings, we herewith submit 2 further Auxiliary Requests.

Auxiliary Request 3 is based on Auxiliary Request 2 and incorporates the limitation of previous claim 10.

Auxiliary Request 4 additionally stipulates that step 3 follows step 2.

A basis for these amendments may be found in Examples 1 to 3 of the description, and as such, they are clearly allowable.

Dr. Alexa von Uexküll
European Patent Attorney

Encl.:
Auxiliary Requests 3 and 4 (marked-up and clean copies)

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EP 02 70 3958.5
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Our Ref.: H2624 EP S3

AUXILIARY REQUEST 3

1. A method for removing contaminant DNA in an antibody-containing sample, which comprises the following steps:
   1) applying the antibody-containing sample to affinity chromatography on Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity of an ionic strength of 0.2 or less ~~or~~ **and** a conductivity of 300 mS/m or less and having a molarity of less than 50 mM, **wherein the acidic aqueous solution has a pH of 1.5 to 3.9**;
   2) adjusting the pH of the resulting eluate to pH 4 **4.3** to ~~8~~ **7.5** by addition of a buffer, wherein the molarity of the adjusted eluate is ~~100~~ **50** mM or less; and
   3) removing the resulting particles **by filtration through a filter**.

2. The method according to claim 1, wherein the acidic aqueous solution is selected from aqueous solutions of hydrochloric acid, citric acid and acetic acid.

~~3. The method according to claim 2, wherein the acidic aqueous solution has a pH of 1.5 to 3.9.~~

43. The method according to any one of claims 1 ~~to 3~~**or 2**, wherein the contaminant DNA is present at a DNA concentration of 22.5 pg/ml or less in the treated sample containing an antibody.

~~5~~4. The method according to claim 1, wherein the buffer is an aqueous solution of Tris.

~~6. The method according to claim 1, wherein the buffer is added to raise the pH to 4.3 to 7.5.~~

~~7~~5. The method according to claim 1, wherein the antibody is a humanized monoclonal antibody.

~~8~~6. The method according to claim ~~7~~5, wherein the antibody is a humanized anti-IL-6 receptor antibody.

~~9~~7. The method according to claim ~~7~~5, wherein the antibody is a humanized anti-HM1.24 antigen monoclonal antibody.

~~10~~8. The method according to claim ~~7~~5, wherein the antibody is a humanized anti-parathyroid hormone-related peptide antibody (anti-PTHrP antibody).

~~11~~9. The method according to claim ~~7~~5, wherein the antibody is a humanized anti-tissue factor antibody.

~~12. The method according to claim 1, wherein the particles are removed by filtration through a filter.~~

~~13~~10. A method for manufacturing a purified antibody, which comprises the steps of the method according to claim 1.

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06. Okt. 2015

AUXILIARY REQUEST 4

1. A method for removing contaminant DNA in an antibody-containing sample, which comprises the following steps:
   1) applying the antibody-containing sample to affinity chromatography on Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity of an ionic strength of 0.2 or less ~~or~~ **and** a conductivity of 300 mS/m or less and having a molarity of less than 50 mM, **wherein the acidic aqueous solution has a pH of 1.5 to 3.9;**
   2) adjusting the pH of the resulting eluate to pH ~~4~~ **4.3** to ~~8~~ **7.5** by addition of a buffer, wherein the molarity of the adjusted eluate is ~~100~~ **50** mM or less; ~~and~~**followed by**
   3) removing the resulting particles **by filtration through a filter**.

2. The method according to claim 1, wherein the acidic aqueous solution is selected from aqueous solutions of hydrochloric acid, citric acid and acetic acid.

~~3. The method according to claim 2, wherein the acidic aqueous solution has a pH of 1.5 to 3.9.~~

~~4~~3. The method according to any one of claims 1 ~~to 3~~**or 2**, wherein the contaminant DNA is present at a DNA concentration of 22.5 pg/ml or less in the treated sample containing an antibody.

~~5~~4. The method according to claim 1, wherein the buffer is an aqueous solution of Tris.

~~6. The method according to claim 1, wherein the buffer is added to raise the pH to 4.3 to 7.5.~~

~~7~~5. The method according to claim 1, wherein the antibody is a humanized monoclonal antibody.

~~8~~6. The method according to claim ~~7~~5, wherein the antibody is a humanized anti-IL-6 receptor antibody.

~~9~~7. The method according to claim ~~7~~5, wherein the antibody is a humanized anti-HM1.24 antigen monoclonal antibody.

~~10~~8. The method according to claim ~~7~~5, wherein the antibody is a humanized anti-parathyroid hormone-related peptide antibody (anti-PTHrP antibody).

~~11~~9. The method according to claim ~~7~~5, wherein the antibody is a humanized anti-tissue factor antibody.

~~12. The method according to claim 1, wherein the particles are removed by filtration through a filter.~~

~~13~~10. A method for manufacturing a purified antibody, which comprises the steps of the method according to claim 1.

In the matter of European Patent Application No. 02703958.5 - 2405
Published as EP1380589
in the name of Chugai Seiyaku Kabushiki Kaisha

THIRD PARTY OBSERVATIONS PURSUANT TO ARTICLE 115 EPC

1 INTRODUCTION

These submissions are made in support of the Examining Division's summons to attend oral proceedings dated 3 June 2015 and take account of the Applicant's submissions in reply dated 3 September 2015.

Also enclosed in support of these submissions are selected pages from Moore, Physical Chemistry (1972).

2 MAIN REQUEST

Claim 1 currently on file is derived from original claim 3, directed to affinity chromatography based methods for producing an antibody-containing sample from which DNA contamination has been removed.

2.1 LACK OF NOVELTY IN VIEW OF D3 (WO95/22389)

Third party observations were filed on 4 April 2008 citing WO 95/22389 (hereinafter "D3") as a novelty destroying disclosure. We agree with those submissions.

In their submissions of 19 April 2010, the Applicant attempted to distinguish the claimed subject matter from D3 with reference to the requirement that the molarity of the adjusted eluate is "0 to 100 mM".

This feature does not, in fact, distinguish the claim from D3. Moreover, as correctly identified by the Examiner, this technical feature introduced into the claim does not find basis in the application as filed:

2.1.1 THE APPLICANT'S INTERPRETATION OF D3 IS ERRONEOUS

The Applicant has submitted that D3 does not disclose the feature that the molarity of the adjusted eluate is 100 mM or less. However, the justification for this position is entirely misleading.

The Applicant contends that the eluate from D3 contains a column volume of the wash buffer, which has a much higher molarity (270 mM) than the elution buffer (25 mM). This is nonsensical and entirely inconsistent with the disclosure of Shadle for several reasons:

1. D3 describes concentration of the target protein in the elution buffer explicitly (page 14 lines 25 to 28) and not in a mixture of wash buffer and elution buffer
2. D3 describes, under the heading "Pooling Criteria", pooling of the eluate fractions from the Protein A capture which are based on UV tracing of the chromatogram (page 17 lines 3 to 5). Thus, the experiments require collection of distinct fractions on the basis of observing the protein peak (i.e. once the peak was observed, collection in a separate vessel would begin). The eluate fractions would certainly *not* include a column volume of wash buffer because the wash buffer fractions would not contain the protein and were not pooled.
3. Moreover, the "entire peak" is collected (page 17 lines 3 to 5) meaning that the elution buffer would flow through the column (and be pooled) until no more protein was eluted.
4. D3 describes in Example IA an elution by applying 15-20 litres of elution buffer and production of a final eluate of approximately 15 litres in volume (page 19 lines 9 to 13). Similarly D3 describes in Example ID an elution by applying 15-20 litres of elution buffer and production of a final eluate of approximately 9 litres in volume, per cycle (page 29 lines 10 to 14). The volumes of elution buffer applied, as compared to the volume of final eluate, are greater and therefore consistent with the eluate containing the protein only in the elution buffer.

Thus, a skilled person would directly and unambiguously derive from D3 that the eluate is composed of the elution buffer (containing the eluted antibody).

Following step 2) of claim 1, D3 also discloses adjusting the pH of the eluate to 5.5 by adding 350 ml of 1 M Tris base in Example IA (page 19 lines 16-17) and by adding 250 ml of 1 M Tris base in Example ID (page 29 line 16). In contrast to the patent application, D3 provides sufficient information to calculate the molarity of the pH adjusted eluate:

In the case of Example IA:

The eluate of 15 litres is 25 mM citrate and has a pH of around 3.5
The volume of 2.5 M HCl needed to adjust the pH to 3.5 is therefore minimal
Subsequent adjustment to pH 5.5 requires the addition of 350 ml of 1 M Tris. This is 350 mmol in 15.35 litres, giving a concentration of 23 mM Tris.
Thus, the total molarity of the pH adjusted eluate is 25 mM (citrate) + 23 mM (Tris) = **48 mM**

In the case of Example ID:

Each eluate of 9 litres is 25 mM citrate and has a pH of around 3.5
The volume of 2.5 M HCl needed to adjust the pH to 3.5 is therefore minimal
Subsequent adjustment to pH 5.5 requires the addition of 250 ml of 1 M Tris. This is 250 mmol in 9.25 litres, giving a concentration of 27 mM Tris.
Thus, the total molarity of the pH adjusted eluate is 25 mM (citrate) + 27 mM (Tris) = **52 mM**

Accordingly, in direct contrast to the misleading analysis provided by the Applicant, D3 directly and unambiguously discloses a pH adjusted eluate with a molarity of less than 100 mM.

2.1.2 ALL TECHNICAL STEPS REQUIRED FOR DNA REMOVAL ARE DISCLOSED IN D3

In the Examination Report dated 24 January 2013, the Examiner appears to have accepted the contention that D3 does not disclose a method for removing contaminant DNA. The Examiner thus suggests that removal of contaminant DNA is a separate technical feature from step 3) of claim 1, which relates to particle removal for example by applying the sample to a filter. We direct the Examiner's attention to the fact that DNA removal with the particles is a mere discovery in the context of the process known from D3.

As discussed in the Third Party Observations of 4 April 2008, step 3) of claim 1 is clearly disclosed in D3 because D3 discloses filtration of the pH adjusted eluate in order to remove particles that are greater than 0.2 µM (page 14 line 35 to page 15 line 2 of D3). It is noted that the Examples of the application also utilise filters of 0.2 µM in order to remove particles.

It is confirmed in the Guidelines for Examination (F, IV, 4.13) that where the claim is directed to a method or process aiming at a certain purpose, when it comprises physical steps which result in the production of a product (i.e. the claim is in fact directed towards the production of a product), the indication of the intended purpose of the method (production of a product) is to be understood in the sense that the method or process has to be merely suitable for that use, rather than comprising the use as an integral method step. Consequently, a prior disclosure of the same method without an explicit indication of the particular purpose (product production), although the method is nevertheless suitable for it, would anticipate a claim to the method for that particular purpose (see T 304/08, confirmed in T 1039/09 and T 428/09). In the present case, claim 1 is directed to production of an antibody containing sample from which DNA contamination has been removed. See also claim 11 which is directed to a method of manufacturing a purified antibody. The fact that the method of D3 represents a disclosure of

all technical steps of claim 1 and would necessarily also result in removal of DNA contamination from the antibody containing sample results in a lack of novelty for claim 1.

2.1.3 THE FEATURE OF IONIC STRENGTH OR CONDUCTIVITY OF THE ELUTION SOLUTION CANNOT GENERATE NOVELTY OVER D3

It is noted that the summons acknowledges novelty over D3 due to the introduction of specific ionic strength and/or conductivity ranges for the elution solution. However, each of these parameters is disclosed in D3. As evidenced below, D3 describes an acidic aqueous solution with an ionic strength of 0.01959 M (i.e. "0.2 or less") and a conductivity of around 150 mS/m (i.e. "300 mS/m or less"). Moreover, the specific ionic strength and conductivity ranges for the elution solution constitute added subject matter when combined with the molarity parameter. Further, the parameters are unclear and insufficiently disclosed in the application.

2.1.3.1 THE IONIC STRENGTH AND CONDUCTIVITY PARAMETERS ARE NOT DISCLOSED IN COMBINATION WITH MOLARITY OF THE ACIDIC AQUEOUS SOLUTION

Step 1) of claim 1 specifies that "the acidic aqueous solution" has various properties. They include (although the claim language is ambiguous as the Examiner has correctly noted), in the alternative:

a. a pH of 1.5 to 3.9 in combination with a low conductivity of an ionic strength of 0.2 or less and a molarity of less than 50mM; or
b. a pH of 1.5 to 3.9 in combination with a conductivity of 300 mS/m or less and a molarity of less than 50mM.

The basis offered for the amendments to generate this combination of subject matter is claims 3, 4, 5, 6 and 8 and page 11 lines 10 to 20.

Firstly, none of these passages provide basis for the "or less" claim language to the extent that the Applicant alleges that this amendment excludes 0 from the claims. For each parameter, ranges between 0 and the upper limit represent the only relevant disclosure.

Secondly, there is no disclosure of an acidic aqueous solution defined by the *combination* of ionic strength *and* molarity parameters, or the conductivity *and* molarity parameters respectively. In the original disclosure all of these parameters are defined as alternatives; claims 4, 5 and 6 are each singly dependent and the description similarly uses "or" language.

The claim is in contravention of Article 123(2) EPC and the features representing added subject matter cannot contribute to novelty over D3.

2.1.3.2 THE "IONIC STRENGTH" AND "CONDUCTIVITY" PARAMETERS ARE UNCLEAR AND CANNOT CONTRIBUTE TO NOVELTY

Step 1) of claim 1 includes the option that the acidic aqueous solution has an ionic strength of "0.2 or less".

No units are provided for this parameter and thus the claim is entirely unclear. Moreover, no units are given anywhere in the specification that could clarify what is meant by an "ionic strength of 0.2 or less". As confirmed on page 443 of Moore (enclosed), ionic strength is typically presented in units of molality or molarity. However, the application provides no guidance as to which unit is to be adopted or indeed how 0.2 is expressed at the upper end of the range. For example, taking a molarity value, 0.2 could refer to 0.2 µM, 0.2 mM or 0.2 M etc.

As an alternative to the ionic strength parameter, step 1) of claim 1 also includes the option that the acidic aqueous solution has a conductivity of 300 mS/m or less.

This parameter of the claim is unclear because conductivity depends on several factors, including temperature. As confirmed on page 425, first full paragraph of Moore (enclosed), conductivity increases with temperature. Nowhere in the specification is it clarified at what temperature the conductivity must be measured to determine whether the claim requirements are met.

Each parameter is further unclear because it is not evident how an acidic aqueous solution could possibly have an ionic strength or a conductivity of zero.

Such unclearly defined parameters cannot be used to generate novelty (as discussed in the Guidelines for Examination at G-VI, 6).

It is further noted that there is nothing in the disclosure of the application to suggest that the elution buffer of D3, 25 mM citrate at pH 3.5 would fall outside the claim scope. In fact, Examples 2 and 3 of the application utilised 20 mM aqueous citric acid as elution solution. The burden of proof is with the applicant in such circumstances (T 1764/06, r. 2.12).

Moreover, as a consequence of the unclearly defined parameters there is also a lack of sufficiency of disclosure (Article 83 EPC). As confirmed in the Guidelines for Examination at F-III, 11, where a claim contains an ill-defined parameter (see also F-IV, 4.11), and the skilled person is not able, on the basis of the disclosure as a whole and using his common general knowledge, to identify the technical measures necessary to solve the problem underlying the application at issue, an objection under Art. 83 should be raised.

2.1.3.3 D3 DISCLOSES AN ACIDIC AQEUOUS SOLUTION THAT DISPLAYS THE "IONIC STRENGTH" AND "CONDUCTIVITY" PARAMETERS AS SET FORTH IN CLAIM 1

Notwithstanding the lack of basis, lack of clarity and lack of sufficiency of disclosure, D3 discloses an elution buffer (25 mM citrate, pH 3.5) that meets all of the individual parameter limitations of the acidic aqueous solution defined in claim 1.

Firstly, as set out in the Ionic Strength calculation of Appendix 1, 25 mM citrate, pH 3.5 has an ionic strength of 0.01959 M. This meets the claim limitation of an ionic strength of 0.2 or less.

Secondly, when measured at 25°C, 25 mM citrate, pH 3.5 displayed a conductivity of around 150 mS/m. This meets the claim limitation of a conductivity of 300 mS/m or less.

Accordingly, the ionic strength and conductivity ranges introduced into claim 1 of the Main Request do not generate novelty over D3.

3 AUXILIARY REQUEST 1

Compared to the Main Request, claim 1 of the Auxiliary Request requires that the molarity of the adjusted eluate is 50 mM or less (rather than 100 mM or less).

This amendment manifestly does not address the objections raised in the summons and in these observations. As discussed in relation to the Main Request, Example IA of D3 produces a pH adjusted eluate with a molarity of 48 mM. Thus, the amended claim lacks novelty over D3.

Moreover, the basis offered by the Applicant for this amendment (page 12 lines 20-28) relates to the definition of an "alkaline aqueous solution of low conductivity" and cannot conceivably relate to the pH adjusted eluate with a pH between 4.3 and 7.5.

4 AUXILIARY REQUEST 2

Compared to the first Auxiliary Request, claim 1 of the second Auxiliary Request requires that the acidic aqueous solution has all of the ionic strength, conductivity and molarity parameters in combination (rather than ionic strength and conductivity being presented as alternatives).

This further amendment manifestly does not address the objections raised in the summons and in these observations. The acidic aqueous solution disclosed in D3 meets all of the ionic strength, conductivity and molarity parameters in combination and thus D3 deprives the claims of novelty. In addition, the ionic strength, conductivity and molarity parameters are

only disclosed in the application as alternative ways of defining the acidic aqueous solution. They are never disclosed as a combination. The features thus represent added subject matter.

5 SUMMARY

None of the amendments offered in response to the Summons address the outstanding objections. None of the requests meets the requirements of the EPC for the reasons explained herein. The application must be refused.

SPENCER; Matthew Peter
BOULT WADE TENNANT

2 October 2015

The examination is being carried out on the **following application documents**:

Description, Pages

1-17, 19-24, 26	filed with entry into the regional phase before the EPO			
18, 25	received on	27.10.2003	with letter of	24.10.2003

Claims, Numbers

1-17	received on	05.12.2007	with letter of	04.12.2007

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D2: EP-A-1 020 522

The following document (D) is cited by the Examiner (see Guidelines C-VI, 8.2 and 8.3). A copy of the document is annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D10: WO9522389

1. Amendments (**Article 123(2) EPC**)

No basis can be found in the application as originally filed for the subject-matter of claim 17.

In order to expedite the procedure of the present application the following comments will not take the above objected amendment into account.

2. Novelty (**Article 54 EPC**)

2.1 The argumentation of the applicant with letter of 04.12.2007 can be followed. Present claims 1-17 appear novel over D2.

2.2 An observation by a third party concerning the present application were filed on 04.04.2008 which was transmitted by the EPO to the applicant with letter of 16.04.2008.

For the reasons outlined in said observations, present claims 1-6, 8-10 and 15-17 are not novel over D3. The applicant is requested to comment on the observations.

3. Inventive step (**Article 56 EPC**)

For the reasons outlined in the above mentioned observations by a third party, present claims 1-17 are not inventive over D3.

4. Sufficiency of disclosure and support in the description (**Articles 83/84 EPC**)

4.1 The objection is maintained in its entirety that the application does not provide adequate guidance to perform the methods of claims 1 and 2 for the reasons outlined in the previous communication. The specification does not show that the use of an aqueous solution of pH 4 to 8 with a low conductivity alone without a prior step of affinity chromatography is sufficient to remove DNA contamination from an antibody-containing sample.

The applicant states with letter of 04.12.2007 that the state of a solution prior to adjusting the solution to pH 4 to 8 under low conductivity is not critical for the formation of DNA-containing particles. However, the applicant did not provide evidence for this statement.

Therefore, the present specification still fails to technically support the whole area claimed and claims 1 and 2 not limited to sufficiently disclosed methods are not enabled and also not supported by the description.

4.2 The subject-matter of claim 17 is neither sufficiently disclosed nor technically supported by the description. The application is silent about manufacturing a medicament comprising a purified antibody.

5. Non-Unity (**Article 82 EPC**)

The objection as to lack of unity was overcome by the amended claims.

6. The applicant is requested to file new claims which take account of the above comments. However, the attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (**Article 123(2) EPC**).

Handwritten amendments may be submitted, however, an additional retyped version of the amended claims is requested. The applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

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Application No.	Ref.	Date
02 703 958.5 - 2405	H 2624 EP S3	23.10.2009
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Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Sommer, Birgit
Primary Examiner
For the Examining Division

Enclosure(s): 3 page/s reasons (Form 2906)
D10

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Munich, April 4, 2008

Our Ref.: AV2008-320 m7/ng
European Patent Application No. 02 703 958.5
Chugai Seiyaku Kabushiki Kaisha

THIRD PARTY OBSERVATIONS PURSUANT TO ART. 115 EPC

The attention of the Examining Division is drawn to an additional previously not cited prior art document, which is relevant for the patentability of the subject matter of the above identified European patent application **EP 02 703 958.5**, which has been published as **EP 1 380 589 A1**. Citations in the following analysis refer to said published application.

The enclosed document that is highly relevant for the patentability of the above-captioned patent application is **WO 95/22389** (corresponding to **EP 0 746 398**), which has been published on 24 August 1995.

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1. EP 02 703 958.5

The above-captioned application has been filed as an international application on 11 March 2002 and claims priority of 9 March 2001.

The currently pending claims have been submitted on 4 December 2007 in response to an official communication dated 9 August 2007. The following analysis of the patentability of said claims is made with current claim 3 as an example.

1.1 Claim 3

Claim 3 of the currently pending set of claims reads:

"*A method for removing contaminant DNA in an antibody-containing sample, which comprises the following steps:*

1) applying the antibody-containing sample to affinity chromatography on Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity having a molarity of 0 to 100 mM;

2) adjusting the pH of the resulting eluate to pH 4 to 8 by addition of a buffer, wherein the molarity of the adjusted eluate is 0 to 100 mM; and

3) *removing the resulting particles.*"

1.1.1 Step 1

In paragraph [0023] of **EP 1 380 589**, Step 1 of the purification method of e.g. pending claim 3 is discussed.

Precisely, it is indicated that:

> "*A sample containing a physiologically active protein is converted into an acidic aqueous solution of low conductivity, preferably by eluting the sample from Protein A/G affinity chromatography with an*

acidic aqueous solution of low conductivity. As used herein, an "acidic aqueous solution of low conductivity" generally refers to an aqueous solution of pH 1.5 to pH 3.9...." (page 5, lines 5 to 9).

The prior art document published as **WO 95/22389** also discloses methods for the purification of antibodies. Please refer to the disclosure at page 14 where the purification process of culture fluid containing an antibody is described.

According to lines 15 to 23, IgG is recovered from the cell-free culture fluid (CCF; as defined at page 13, lines 21 to 22) by adsorption chromatography on a column of ProSepA, i.e. by Protein A chromatography (page 14, line 25 as well as claim 9).

Thereafter, the bound IgG clone RSHZ-19 (a definition for this antibody clone is found at page 13, lines 3 to 7) is eluted with a low pH buffer (page 14, line 22) using Elution Buffer. The composition of said Elution Buffer is described at page 18, Table 1. It consists of 25 mM citrate, pH 3.5. It should also be noted that the Protein A chromatography is performed to remove impurities such as DNA (page 14, line 26, and page 7, line 16). The low pH buffer used in this step corresponds to the "*acidic buffer*" in claim 3, step 1, of **EP 02 703 958.5**.

It follows that all features in step 1 of current claim 3 of the application **EP 02 703 958.5** are disclosed in **WO 95/22389**.

1.1.2 Step 2

The method described in **WO 95/22389** also anticipates step 2 of the method in claim 3 of **EP 02 703 958.5**.

Reference may be made to page 14, lines 32 to 35 of said prior art document, which read:

*"The Protein A column eluate is collected and adjusted to pH 3.5 by the addition of 2.5 M HCl. The solution is transferred to a second vessel and held a pH 3.5 for at least thirty minutes to provide viral inactivation, and **readjusted to pH 5.5** by the addition of **Tris buffer**."*
[Emphasis added]

This step corresponds to pH adjustment in step 2 of claim 3 of **EP 02 703 958.5**.

In this respect, reference may be made also to the disclosure at page 5, paragraph [0024] of **EP 1 380 589**. Lines 17 to 20 disclose that the acidic eluate after applying the antibody-containing sample to a Protein A affinity column is

> *"...then **neutralized** by addition of a buffer to raise the pH to **a neutral level**. A buffer added at this stage includes, for example, **Tris-HCl** buffer...."* [Emphasis added]

Thus, the buffer used in **WO 95/22389** is identical to one of the buffers suggested for use in **EP 02 703 958.5**.

Moreover, according to page 5, lines 20 to 22, **EP 02 703 958.5**,

> *"A neutral level will vary depending on the type of physiologically active protein or antibody to be purified. It usually ranges from **pH 4 to pH 8**...".* [Emphasis added]

Thus, the pH level suggested in **EP 02 703 958.5** comprises the value disclosed in **WO 95/22389**, since pH 5.5 is encompassed by the range mentioned in step 2 of claim 3. Consequently, the features of said step have been described in the prior art document.

1.1.3 Step 3

Step 3 of present claim 3 of **EP 02 703 958.5** is directed to the removal of resulting particles of the previous steps.

First, it must be emphasized that **WO 95/22389** discloses step 1 and step 2 of the application **EP 02 703 958.5**. Therefore, it can only be concluded that particles were formed also when performing the same steps in **WO 95/22389**.

The nature of the particles after the neutralization step and their removal is better defined in paragraphs [0026] to [0030] at page 5 of the A1-publication of **EP 02 703 958.5**.

Precisely, paragraph [0026] states that

> *"According to the present invention, the solution neutralized to a neutral pH level in the above stage, in turn, produces particles [...]. These particles may be removed by filtration through a filter to ensure efficient removal of contaminant DNA. Examples of a filter available for filtration include, but are not limited to, a 1.0-0.2 μm Cellulose Acetate Filter System (Corning) or TFF."*

The last sentence bridging pages 14 and 15 of **WO 95/22389** discloses that the neutralized solution is filtered through a prefilter and a sterilized 0.2 μm filter.

Thus, in both, **EP 02 703 958.5** and **WO 95/22389**, the neutralized eluates containing antibodies are filtered. Whether or not it was known that the filtration step removes particles is irrelevant, since the effect is the same.

In **WO 95/22389**, the Protein A eluate is further purified by cation exchange chromatography to remove protein and non-protein impurities (page 15, lines 8 to 15), followed by hydrophobic interaction chromatography (page 16, lines 1 to 15) and finally by re-filtration using tangential-flow ultrafiltration (with a 30,000 molecular weight cut-off filter, diafiltration and sterile filtration using 0.2 micron filter step. Thus, a further filtration step using the same pore size as in **EP 02 703 958.5** is performed.

Consequently, the method disclosed in **WO 95/22389** also comprises step 3 of the method claimed in **EP 02 703 958.5**.

It should be noted that the particles removed in step 3 of the discussed method may alternatively also be removed by centrifugation or any other techniques for efficient particle removal; procedures are not limited to filtration through a filter (refer to page 5, para. [0027] of **EP 02 703 958.5**).

The inventors of said application hypothesize that Protein A/G column chromatography alone is not sufficient to ensure effective separation between contaminant DNA and physiologically active protein because DNA-protein conjugates are formed on the column resin, as suggested in paragraph [0029].

The following paragraph [0030] proposes using further chromatographic purification steps such as cation-exchange chromatography, etc. These methods are also performed in **WO 95/22389**, as discussed above.

2. Conclusions

It follows from the above analysis that the subject matter of the set of claims of **EP 02 703 958.5** presently under examination is not patentable, since all steps of present claim 3 are disclosed in the cited prior art document. **Claim 3** is therefore not novel in the sense of Art. 54 EPC

The above analysis has been made by comparison of pending claim 3 and the disclosure in **WO 95/22389**. However, since the method of claim 3 is merely a preferred embodiment of the methods according to pending **claims 1** and **2**, it is clear that these claims are not novel either, since the disclosure of a specific embodiment also anticipates more generalized claims.

As far as the remaining **claims 4 to 17** of the set of claims submitted on 4 December 2007 with respect to **EP 02 703 958.5** are concerned, these are either not novel or inventive for the following reasons:

Present **claim 4** indicates that the acidic aqueous solution has a molarity of 0 to 50 mM. The elution buffer in **WO 95/22389** is 25 mM citrate buffer (page 18, Table 1). The subject matter of claim 4 is therefore not novel.

Present **claim 5** states that the acidic aqueous solution is selected from aqueous solutions of hydrochloric acid, citric acid and acetic acid. Since, the elution buffer in **WO 95/22389** is 25 mM citrate buffer, the subject matter of claim 5 is partially not novel. The remaining two alternatives relate to commonly used acids in the field of molecular biology. The application does not provide any evidence for a surprising technical effect associated their use. Thus, these acids are only equivalents to the citrate buffer in the prior art, which renders them not patentable under Art. 56 EPC.

Present **claim 6** indicates that the acidic aqueous solution has a pH of 1.5 to 3.9. The elution buffer used in the cited prior art has a pH of 3.5 (page 18, line 10). Thus, claim 6 is not new.

Present **claim 7** points out that the amount of DNA after conducting the methods in the preceding claims is 22.5 pg/ml or less. In the absence of any beneficial technical effects associated with this amount compared to the closest prior art methods (such as those in **WO 95/22389**), the indicated value can only be considered as an arbitrary choice. Claim 7 is not inventive.

Present **claim 8** specifies the buffer in the aqueous solution as Tris buffer, and present claim 9 defines the pH value of 4.3 to 7.5. In **WO 95/22389** Tris buffer is used as well, and the pH after addition of the buffer is adjusted to pH 5.5 (page 14, line 35). Therefore, the subject matter of claims 8 and 9 is anticipated.

Present **claim 10** indicates that the antibody is a humanized monoclonal antibody. In **WO 95/22389** a humanized IgG against Respiratory Syncytial Virus (page 13, lines 3 to 7. Thus, the subject matter of claim 10 does not fulfil the requirements of Arts. 54 and 56 EPC.

Present **claims 11** to **14** relate to humanized antibodies having particular specificities, e.g. for IL-6, HM1.24, parathyroid hormone related peptide, and tissue factor. There is no disclosure in **EP 02 70 3985.5**, which demonstrates that it was surprising that such antibodies could be purified with an already established method for the purification of humanized antibodies. Thus, the subject matter in these claims are obvious variations of the method disclosed in **WO 95/22389**.

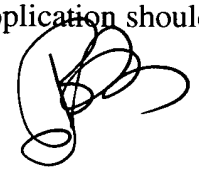
Present **claim 15** indicates that the particles in claims 1 to 3 are removed by filtration. This is also the case in **WO 95/22389** (refer to page 14, last sentence bridging to page 15). Claim 15 lacks novelty.

Present **claim 16** relates to a method for manufacturing a purified antibody, which comprises the methods of claims 1 to 3. This claim does not contain any features that have not been disclosed in **WO 9572389**, wherein a purified antibody is prepared. Claim 16 is not new.

Present **claim 17** is a second medical use claim, referring to the method of purification in claim 16 in the manufacture of a medicament. Since it is clear that the antibodies purified in **WO 95/22389** are directed to a virus having humanshosts, the subject matter is not novel or inventive (refer also to the

disclosure at page 6, lines 23 to 26, which relate to the use of antibodies in prevention and therapy of RSV infections).

In light of the above, none of the claims of **EP 02 703 958.5** is patentable. The application should therefore be refused under Art. 97(2) EPC.



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Enc. WO 95/22389