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80298 M U N I C H

EP 10 01 1215.0-1410
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP/1 S3

München, August 25, 2016
UEX/MW/KSY

Further to our formal Notice of Appeal against the decision of April 25, 2016 to refuse European patent application No. 10 01 1215.0 filed on June 13, 2016, we herewith provide our statement setting out the grounds of appeal in accordance with Article 108 and Rule 99 EPC.

1. REQUESTS

It is requested that the decision of April 25, 2016 to refuse European patent application No. 10 01 1215.0 be set aside and that the application be granted based on the Main Request filed in the first instance on March 18, 2016.

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 Main Request as filed in the first instance on March 18, 2016, Applicant requests permission to submit further requests.

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2. ARTICLE 123(2) EPC

According to the Board, claim 1 of the Main Request on file does not meet the requirements of Article 123(2) EPC, as not all features of the method are directly and unambiguously disclosed in the application as filed (item 1.1.1 of the Reasons of the decision).

In particular, the Board stated under item 1.1.3 that no basis for the features of converting a protein sample into an acidic aqueous solution having

a) a molarity of 50 mM or less and

b) a pH of 2.0 to 3.9 and adjusting the pH of the resulting sample to

c) a pH of 4.3 to 7.5

can be found. According to the Board, even if the selected ranges a) to c) are present in the application as filed as possible alternatives, e.g., in original claim 2, the specific combination is not disclosed in this individualized form, and constitutes and inadmissible specific combination of items from three different lists of features obtained by the selection of a molarity of 50 mM or less for a) (first list), a selection of a pH of 2.0 to 3.9 from a second list for b) and the selection of possible for pH values for c) (third list).

It is submitted that independent claim 1 is directed to a method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises converting the sample into an acidic aqueous solution of low conductivity having a molarity of 50 mM or less and a pH of 2.0 to 3.9, adjusting the pH of the resulting sample to pH 4.3 to 7.5 by addition of a buffer and removing the resulting particles.

In this context, the Board is pointed to the disclosure of the specification as filed on page 11:

> "As used herein, an "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 [...]." (Emphasis added)

The ranges for molarity and pH cited in claim 1 are based on the passage referred to above, and the ranges "pH 2.0 to pH 3.9" and "0 to 50 mM" are referred to as "preferably", i.e. of the same level of preference. Thus, the description clearly discloses the combination of the ranges "pH 2.0 to pH 3.9" and "0 to 50 mM" regarding the acidic aqueous solution as a preferable option in step 1) of claim 1. Furthermore, the specification as filed discloses on page 12:

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> "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, preferably pH 4.3 to pH 7.5, and more preferably pH 4.5 to pH 7.5." (Emphasis added)

As indicated above, the range pH 4.3 to pH 7.5 of the resulting sample is referred to as a preferable option, again at the same level of preference. Thus, the features of the conditions of the acidic solution in step 1) and the resulting sample in step 2) of claim 1 is unambiguously disclosed in the specification as filed as a preferable option.

It is submitted that the Applicant by combining these embodiments of the three features of the same level of preference only has done something that any real-world skilled person automatically does when reading a document.

When a document discloses three features in combination and one preferred embodiment for each feature, a skilled person would certainly not conclude that a combination of these preferred features is not part of the disclosure of this document. Contrary to the position taken by the Examining Division, this combination of features does not constitute an arbitrary selection of features and is directly and unambiguously derivable from the application as filed.

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

3. ARTICLE 76 EPC

In view of the above, the application also meets the requirements of Article 76 EPC.

4. ARTICLES 54 AND 56 EPC

We submit that the subject-matter of the Main 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.

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5. ARTICLE 83 IN COMBINATION WITH ARTICLE 84 EPC

It is submitted that the application meets the requirements of Article 83 in combination with Article 84 EPC.

Full reference is made to our submissions in the first instance.

6. ARTICLE 84 EPC

It is submitted that it is clear for a mind willing to understand that an acidic aqueous solution of low conductivity (i.e. having a molarity of 50 mM or less) cannot not have molarity of zero and that thus such a solution is not covered by the claim.

In this context, it is noted that in the parent case (EP 02 70 3958.5), the Examining Division under item 1.2.1 of the decision of March 17, 2016 stated that the nature of the acidic solution in step 1) should be clear.

Furthermore, it is submitted 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 50 mM or less in the acidic aqueous solution (of low conductivity) of claim 1, step 1). Step 2) of claim 1 does not cite any molarity.

In view of the above explanations, the claims of the Main Request should meet the requirements of Article 84 EPC.

Dr. Alexa von Uexküll
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Application No.	Ref.	Date
10 011 215.0 - 1410	H2624 EP/1 S3	25.04.2016
Applicant Chugai Seiyaku Kabushiki Kaisha		

Decision to refuse a European Patent application

The Examining Division - at the oral proceedings dated 19.04.2016 - has decided:

European Patent application No. 10 011 215.0 is refused.

Applicant/s:
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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.

Registered letter with advice of delivery
EPO Form 2007 12.07TRI

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Enclosure(s): 5 page/s reasons (Form 2916)
Form 2019
MR, AR1-4 of 18.03.2016

to EPO postal service: 20.04.16

Summary of Facts and Submissions

1 European patent application No. 10 011 215.0 having the title "Protein purification method" was filed on 11.03.2002 and is a divisional application of European patent application No. 02 703 958.5. It claims priority of JP 2001067111 filed on 09.03.2001 and was published as EP2336149 on 22.06.2011. The applicant is CHUGAI SEIYAKU KABUSHIKI KAISHA, JP.

2 The European search opinion cited the documents

D1 LYDERSEN B K et al., ANN. N Y ACAD. SCIE., vol. 745, 1994, pages 222-231

D2 EP 1 020 522 A

D3 WO 95/22389 A1

D4 SHINKURA H et al., TOXICOL., vol. 122,1997, pages 163-170

D5 EP 0 962 467 A

and raised objections under **Articles 54, 56, 82, 83/84** and **84 EPC**.

3 The applicant provided argumentation and an amended set of claims with letter of 22.12.2011. 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 17.04.2012 and raised or maintained objections under **Article 84 EPC**.

4 With letter of 19.10.2012, the applicant provided argumentation and an amended set of claims. The examining division provided a detailed response on 25.01.2013 and raised or maintained objections under **Articles 56, 83/84** and **84 EPC**.

5 The applicant provided argumentation and amended sets of claims with letter of 30.07.2013.

6 On 19.10.2015 the examining division summoned the applicant to oral proceedings according to **Rule 115 EPC** to be held on 19.04.2016 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.

7 The applicant responded to the summons with letter of 18.03.2016 and submitted a Main Request as well as Auxiliary Requests 1-4. With letter of 12.04.2016, the applicant submitted additional experimental data. The

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examining division informed the applicant with communication of 26.04.2016 (faxed in advance on 14.04.2016) that objections under **Articles 54, 83/84, 84** and/or **123(2) EPC** are maintained against all requests on file.

8 Oral proceedings were held on 19.04.2016. 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, 2, 7, 8, 13, 15-29	as originally filed			
3-6, 9-12, 14	received on	22-10-2012	with letter of	19-10-2012

Claims, Numbers

1-8	received on	18-03-2016	with letter of	18-03-2016

Auxiliary Request 1

Description, Pages

1, 2, 7, 8, 13, 15-29	as originally filed			
3-6, 9-12, 14	received on	22-10-2012	with letter of	19-10-2012

Claims, Numbers

1-8	received on	18-03-2016	with letter of	18-03-2016

Auxiliary Request 2

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Description, Pages

1, 2, 7, 8, 13, 15-29	as originally filed			
3-6, 9-12, 14	received on	22-10-2012	with letter of	19-10-2012

Claims, Numbers

1-8	received on	18-03-2016	with letter of	18-03-2016

Auxiliary Request 3

Description, Pages

1, 2, 7, 8, 13, 15-29	as originally filed			
3-6, 9-12, 14	received on	22-10-2012	with letter of	19-10-2012

Claims, Numbers

1-8	received on	18-03-2016	with letter of	18-03-2016

Auxiliary Request 4

Description, Pages

1, 2, 7, 8, 13, 15-29	as originally filed			
3-6, 9-12, 14	received on	22-10-2012	with letter of	19-10-2012

Claims, Numbers

1-7	received on	18-03-2016	with letter of	18-03-2016

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

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1 **Main Request:**

Independent claim 1 concerns a method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises converting the sample containing a physiologically active protein into an acidic aqueous solution having a molarity of 50 mM or less and a pH of 2.0 to 3.9, adjusting the pH of the resulting sample to a pH 4.3 to 7.5 and removing the resulting particles.

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

1.1.1 The objection was made that the method of claim 1 including all its features is no directly and unambiguously disclosed in the application as originally filed.

1.1.2 The applicant cited original claims 2, 4,6, 8 and 11 as well as passages on page 11, lines 12-16, and page 12, lines 12-16 of the description as alleged basis. The applicant further argued that the amendments are all based on preferred embodiments. A selection of only preferred embodiments is envisaged by the general method and does not represent a combination of unrelated embodiments.

1.1.3 This argumentation cannot be followed for the following reasons:

No basis can be found in the application as originally filed for the method of claim 1 comprising the features of converting a protein sample into an acidic aqueous solution having a) a molarity of 50 mM or less and b) a pH of 2.0 to 3.9 and adjusting the pH of the resulting sample to c) a pH of 4.3 to 7.5. Even if the selected ranges a)-c) are present in the application as originally filed as possible alternatives of e.g. original claim 2, the specific selection referred to in present claims 1-8 is not disclosed in the application as originally filed.

In the context of amendments, 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).

In the present case such a specific combination of items from three different lists of features is obtained by the selection of a molarity of 50 mM or less from a first list of possible molarities (description, e.g. page 11, line 15-17), the selection of a pH of 2.0 to 3.9 from a second list of possible pH values (description, e.g. page 11, line 13-15) and the selection of a pH of 4.3 to 7.5 from a third list of possible pH values (description, e.g. page 12, line 14-16).

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The argument that only preferred embodiments are selected is not deemed persuasive. The selection of specific features from different embodiments is considered as a combination of features, irrespective of whether said embodiments are preferred ones or not. Moreover, the claimed ranges for each of features a)-c) are actually not the most preferred ones, but the middle range out of three preferred and most preferred ranges.

The content of a document cannot be viewed as a reservoir from which features pertaining to separate embodiments could be combined in order to artificially create a particular embodiment. When assessing wether a feature had been disclosed in a document, the relevant question is whether a skilled person would seriously contemplate combining the different features cited in that document (**T296/96**). That is not the case in the present application as filed, since there is no direct and unambiguous disclosure that the method of claim 1 with its specific combination of features is intended as a preferred embodiment.

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

2 **Auxiliary requests 1-4:**

The argumentation outlined above applies *mutatis mutandis* to claim 1 of Auxiliary Requests 1-4. All four Auxiliary Requests also contain the passages mentioned above which are objected to as comprising unallowable amendments.

Therefore, none of the four Auxiliary Requests meets the requirements of **Article 123 EPC**.

Decision

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

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ANNEX 1

Preparing hPM-1 by Protein A chromatography

hPM-1 (humanized anti-IL-6 receptor antibody) was prepared from a sample by the steps as shown below.

[Preparation steps]
Load a cell culture filtrate comprising hPM-1 onto Protein A column.
↓
Wash the column with a buffer (pH 7.7±0.3) containing 0.5 mM citric acid and 9.5 mM sodium phosphate.
↓
Elute with 858 L of 2.5 mM HCl (pH 2.7±0.2), and then add 2.0 L of 1 M HCl to the eluate.
↓
Adjust pH of the sample solution with 2.792 L of 1 M Tris solution (pH 7.2)

Total molarities were calculated by volume of buffers actually used. PH values the sample solution were measured by a pH meter. Presence or absence of DNA particles were observed before and after the pH adjustment step.

[Result]
Table 1. Total molarity, pH, and DNA particle observed

Step	Total molarity	pH	DNA particle
Elution and Acid addition [a)]	4.8 mM [c)]	3.2	No
pH adjustment [b)]	8.0 mM [d)]	7.2	Yes

a) corresponding to step 1) of present Claim 1
b) corresponding to step 2) of present Claim 1
c) 2.5 mM (from 858 L of the eluate) + 2.3 mM (from 2.0 L of 1 M HCl: 2.0/(2.0 + 858) =

4.8 mM)

d) Molarity derived from 1 M Tris solution: 2.792/(860+2.792) = 3.2 mM.

It was observed that the sample solution was clear before the pH adjustment step. No particle was observed before the pH adjustment step (Figures 1A and 1B). However, once pH of the sample was adjusted to 7.2, the sample became turbid (Figures 1C and 1D). This drastic increase of the sample in turbidity was due to development of DNA particles by pH change from 3.2 to 7.2. Those DNA particles can easily be removed by a simple method such as filtration, thereby purifying hPM-1 efficiently.

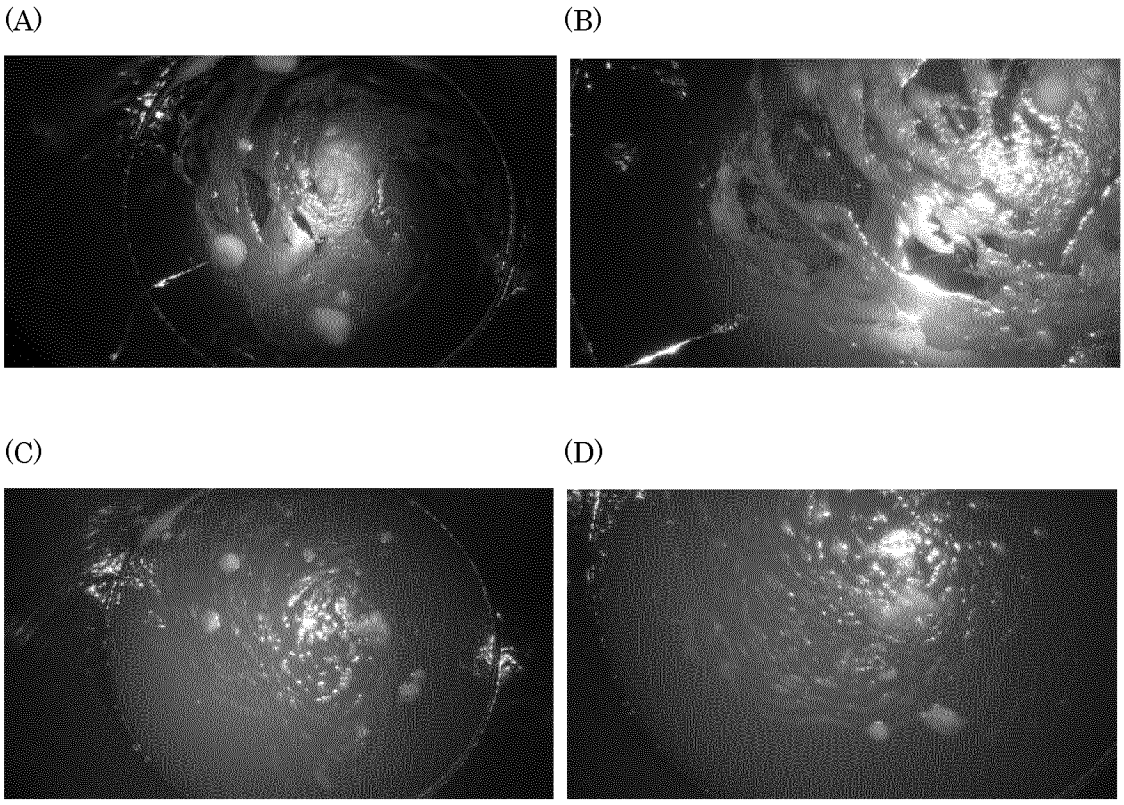

Figure 1. Pictures of a sample solution taken before (A, B) and after pH adjustment step (C, D).

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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	10011215.0
Applicant's or representative's reference	H2624 EP/1 S3

	Description of document	Original file name	Assigned file name
1	Letter dealing with Oral proceedings	H2624 EP_1 S3 Petition.pdf	ORAL-1.pdf
2	Document filed during examination procedure	H2624 EP_1 S3 Annex 1.pdf	EXAM-1.pdf

Signatures

Place:	**Munich**
Date:	**12 April 2016**
Signed by:	**/Dr. Alexa von Uexküll/**
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EP 10 01 1215.0-1410
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP/1 S3

München, April 12, 2016
UEX/MW/KSY

VERY URGENT!

ORAL PROCEEDINGS SCHEDULED FOR APRIL 19, 2016!

This is further to our response to the summons to attend oral proceedings scheduled for April 19, 2016 dated March 18, 2016.

As indicated in section 2.3 of said response, we herewith submit additional experimental data representative of three separate repetitions of experiments demonstrating that contaminant DNA is aggregated to a significant extent by submitting the sample to step 1) and step 2) of claim 1 of the Main Request filed with our submissions of March 18, 2016 (see Annex 1, in particular Figures 1A to 1D). Thereby, efficient removal of contaminant DNA by simple filtration is possible. The prior art neither discloses nor suggests simple DNA removal employing said steps.

In view of the results submitted herewith, demonstrating the drastic visual change of the sample underlying steps 1) and 2) of the method of the

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invention, the objections raised with regard to Article 56 EPC should be rendered moot.

There should thus be no need for oral proceedings and they should be cancelled. 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) 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.:
Annex 1 (Additional experimental data)

PFIZER, INC., IPR2017-01358, Ex. 1011, p. 17 of 60

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18. März 2016

EP 10 01 1215.0
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP/1 S3

~~AMENDED CLAIMS SET~~AUXILIARY REQUEST 1

~~1.~~ A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the following steps:

1) converting the sample containing a physiologically active protein into 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 ~~less than~~ ~~50~~ **30** mM **or less** and a pH of ~~1.5~~**2.0** to 3.9;
2) adjusting the pH of the resulting sample to a pH of **4.3** to ~~8~~**7.5**; 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 claim 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 a physiologically active protein.

4. The method according to claim 1, wherein an aqueous solution of Tris is used to adjust the pH of the resulting sample.

~~5. The method according to claim 1, wherein the pH of the resulting sample is adjusted to pH of 4.3 to 7.5.~~

~~6~~5. The method according to claim 1, wherein the physiologically active protein is an antibody.

~~7~~6. The method according to claim ~~6~~5, wherein the antibody is a humanized monoclonal

antibody.

~~87~~. The method according to claim ~~76~~, wherein the antibody is a humanized anti-IL-6 receptor antibody.

~~98~~. The method according to claim 1, wherein the particles are removed by filtration through a filter.

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~~AMENDED CLAIMS SET~~AUXILIARY REQUEST 3

1. A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the following steps:
   1) converting the sample containing a physiologically active protein into 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 ~~less than~~ ~~50~~ **30** mM **or less** and a pH of ~~1.5~~**2.0** to 3.9;
   2) adjusting the pH of the resulting sample to a pH of **4.5** to ~~8~~**7.5**; 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 claim 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 a physiologically active protein.

4. The method according to claim 1, wherein an aqueous solution of Tris is used to adjust the pH of the resulting sample.

~~5. The method according to claim 1, wherein the pH of the resulting sample is adjusted to pH of 4.3 to 7.5.~~

~~6~~5. The method according to claim 1, wherein the physiologically active protein is an antibody.

~~7~~6. The method according to claim ~~6~~5, wherein the antibody is a humanized monoclonal

antibody.

87. The method according to claim ~~76~~, wherein the antibody is a humanized anti-IL-6 receptor antibody.

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

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~~AMENDED CLAIMS SET~~MAIN REQUEST

1. A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the following steps:
   1) converting the sample containing a physiologically active protein into 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 less than~~ 50 mM **or less** and a pH of ~~1.5~~**2.0** to 3.9;
   2) adjusting the pH of the resulting sample to a pH of **4.3** to ~~8~~**7.5**; 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 claim 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 a physiologically active protein.

4. The method according to claim 1, wherein an aqueous solution of Tris is used to adjust the pH of the resulting sample.

~~5. The method according to claim 1, wherein the pH of the resulting sample is adjusted to pH of 4.3 to 7.5.~~

~~6~~5. The method according to claim 1, wherein the physiologically active protein is an antibody.

~~7~~6. The method according to claim ~~6~~5, wherein the antibody is a humanized monoclonal

antibody.

87. The method according to claim ~~76~~**76**, wherein the antibody is a humanized anti-IL-6 receptor antibody.

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

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EP 10 01 1215.0
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16. März 2016

~~AMENDED CLAIMS SET~~AUXILIARY REQUEST 4

1. A method for removing contaminant DNA in a sample containing ~~a physiologically active protein~~**an antibody**, which comprises the following steps:
   1) converting the sample containing ~~a physiologically active protein~~**an antibody** into 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 ~~less than 50~~ **30** mM **or less** and a pH of ~~1.5~~**2.0** to 3.9;
   2) adjusting the pH of the resulting sample to a pH of **4.3** to ~~8~~**7.5**; 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 claim 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 a physiologically active protein.

4. The method according to claim 1, wherein an aqueous solution of Tris is used to adjust the pH of the resulting sample.

~~5. The method according to claim 1, wherein the pH of the resulting sample is adjusted to pH of 4.3 to 7.5.~~

~~6. The method according to claim 1, wherein the physiologically active protein is an antibody.~~

~~7~~5. The method according to claim ~~6~~1, wherein the antibody is a humanized monoclonal

antibody.

86. The method according to claim ~~71~~, wherein the antibody is a humanized anti-IL-6 receptor antibody.

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

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~~AMENDED CLAIMS SET~~AUXILIARY REQUEST 2

1. A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the following steps:
   1) converting the sample containing a physiologically active protein into 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 ~~less than~~ ~~50~~ **30** mM **or less** and a pH of ~~1.5~~**2.0** to 3.~~9~~**0**;
   2) adjusting the pH of the resulting sample to a pH of **4.3** to ~~8~~**7.5**; 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 claim 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 a physiologically active protein.

4. The method according to claim 1, wherein an aqueous solution of Tris is used to adjust the pH of the resulting sample.

~~5. The method according to claim 1, wherein the pH of the resulting sample is adjusted to pH of 4.3 to 7.5.~~

~~6~~5. The method according to claim 1, wherein the physiologically active protein is an antibody.

~~7~~6. The method according to claim ~~6~~5, wherein the antibody is a humanized monoclonal

antibody.

87. The method according to claim ~~76~~, wherein the antibody is a humanized anti-IL-6 receptor antibody.

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

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18. März 2016

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EP 10 01 1215.0-1410
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Our Ref.: H2624 EP/1 S3

München, March 18, 2016
UEX/MW/KSY

This is in response to the summons to attend oral proceedings dated October 19, 2015.

In preparation of the oral proceedings scheduled for April 19, 2016, we herewith submit a Main Request and Auxiliary Requests 1 to 4, which should form the basis of the further prosecution of the present application.

1. NATURE OF THE AMENDMENTS

1.1. Main Request

The Main Request corresponds to the claims set as filed on July 30, 2013.

However, the acidic aqueous solution in step 1 of claim 1 has been defined as having a molarity of 50 mM or less and a pH of 2.0 to 3.9.

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This amendment is based on the disclosure on page 11, lines 14 to 16.

Furthermore, the pH of the resulting sample in step 2 has been amended by introducing the limitation of previous claim 5.

As a consequence, previous claim 5 has been deleted, the remaining claims have been renumbered and the dependencies amended accordingly.

1.2 Auxiliary Request 1

Auxiliary Request 1 corresponds in essence to the Main Request.

However, the acidic aqueous solution in step 1 of claim 1 has been defined as having a molarity of 30 mM or less.

This amendment is based on the disclosure on page 10, line 17 as filed.

1.3 Auxiliary Request 2

Auxiliary Request 2 corresponds in essence to Auxiliary Request 1.

However, the acidic aqueous solution in step 1 of claim 1 has been defined as having a pH of 2.0 to 3.0.

This amendment is based on the disclosure on page 11, line 15 as filed.

1.4 Auxiliary Request 3

Auxiliary Request 3 corresponds in essence to Auxiliary Request 1.

However, the pH of the resulting sample in step 2 has been amended to cite a pH of 4.5 to 7.5.

This amendment is based on the disclosure on page 10, line 6 as filed.

1.5 Auxiliary Request 4

Auxiliary Request 4 corresponds in essence to Auxiliary Request 1.

However, the physiologically active protein has been defined as an antibody, thereby introducing the limitation of previous claim 6.

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This amendment is based on the disclosure on page 5, item (12).

As a consequence, also previous claim 6 has been deleted.

As none of the above amendments comprises subject-matter extending beyond the present application or the parent application as filed, the Main Request and Auxiliary Requests 1 to 4 should be admissible within the meaning of Articles 123(2) EPC and 76(1) EPC.

2. MAIN REQUEST

2.1 Article 123(2) EPC

In view of the above amendments to claim 1, defining the acid aqueous solution of low conductivity by its pH value and molarity only, based on the disclosure on page 11, lines 12 to 20, in particular lines 14 to 16, the objections raised with regard to Article 123(2) EPC should be rendered moot.

2.2 Article 54 EPC (Novelty)

Contrary to the present invention, D3 is not directed to a method for removing contaminant DNA from a sample. As shown in Example 1 of the present specification, even adjusting the pH from acidic range to neutral range in a solution with high molarity (100 mM NaCl, Table 2) did not lead to precipitation of DNA. As a result, contaminant DNA could not be removed by filtration with a filter. At the filing date of the present application, a person skilled in the art would have understood that DNA cannot be removed by filtration with a filter. This is supported by D3, disclosing that:

> "After neutralizing to pH 5.5, 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" (page 19, lines 17 to 19 of D3).

The filtration step in D3 was known to a person skilled in the art as a typical step for removing bacteria and mycoplasma in a sample. In view of the general knowledge at the filing date and also in view of the disclosure of D3 referred to above, a person skilled in the art would not have considered the method disclosed in D3 to be directed to removing contaminant DNA from a sample. D3 thus provides no disclosure whatsoever of DNA removal from a sample.

Therefore, claim 1 of the Main Request is novel over D3.

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2.3 Article 56 EPC (Inventive step)

The key of the present invention resides in the finding that by adjustment of the pH to a specific range by an aqueous acidic solution while maintaining a conductivity as low as possible (such as a molarity of 50 mM or less) contaminant DNA may be expediently removed from a sample

According to the Examiner, the problem has not been solved over the whole scope of the claims, as the previously pending claims encompassed adjusting the pH of the eluate to pH 4.0, which is shown in the Examples to have a negative effect. The Examiner specifically had pointed to the results from pH 4.0 in Table 3 of Example 2 in comparison to pH 2.7. However, Table 3 clearly shows that the residual DNA was lower at pH 4.0 than that at pH 2.7 after 0 hr- and 6 hr-incubation.

Furthermore, the Examiner raised doubts that a solution of 0 mM molarity results in solving the problem of the present invention; namely, removing a DNA contaminant from a sample. In particular, an objection was raised that a solution cannot have a pH of 4 to 8, while having a molarity of 0 mM.

However, the claims need to be read with the eyes of an expert willing to understand the claimed subject-matter. A person of skill in the art would readily understand that a solution according to the present invention with a certain pH, of course, cannot possibly have a molarity of 0, but would understand that he has to aim at a solution with a molarity as low as possible.

As demonstrated by the turbidity values in Table 2 of the present specification, the method of the present invention induces a drastic visual change to the sample solution by insolubilization of contaminant DNA by merely adjusting the pH from an acidic range to a neutral range. Applicant will also provide additional evidence that supports this point. Thus, the method of the present invention merely requires a simple filtration step to efficiently remove the precipitated contaminant DNA, as specified in claim 8. The method according to the present invention does not need a complex filtration system as disclosed in D3, which uses 0.1 micron filter directly connected to 0.2 micron filter. From the prior art including D3, such an effect of the present invention could not be predicted.

In view of the above amendments to the claims with regard to the pH range and the explanation, the objections raised should thus have been overcome.

Applicant will provide additional experimental data supporting the superior effect of the present invention over the prior art at his earliest convenience.

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

2.4.1 The Examiner considered it not credible that DNA contaminants will precipitate in an aqueous solution of 0 mM, and that it is not possible to adjust the pH 4 to 8 by an aqueous solution of 0 mM molarity.

In view of the arguments submitted in section 2.3, above, this objection should be rendered moot.

2.4.2 The Examiner, moreover, has raised the objection that no example supports the method of claim 1.

Claim 1 as amended in the Main Request cites the molarity of the acid aqueous solution, which is supported by the Examples in the specification. Furthermore, as stated above (section 2.3, inventive step), Table 3 of the specification shows that the removal of DNA contamination was more efficient at pH 4.0 than a pH 2.7.

2.4.3 The Examiner objected that ionic strength and conductivity have not been clearly defined.

In view of the above amendments to the claims, this objection should be rendered moot.

2.5 Article 84 EPC (Clarity)

2.5.1. According to the Examiner, it is not clear to what compounds the term "molarity" relates.

As evidenced by the third party observations, one of skill in the art would have had no problem calculating the molarity in D3. By the same token, a person of skill in the art would readily understand that a molarity of 50 mM or less relates to the total molarity, inter alia, of all components of the aqueous acidic solution of step 1. This is also clear from the disclosure of the specification in lines 8 to 20 of page 11, disclosing that the resulting acidic aqueous solution has a molarity of preferably 50 mM or less (i.e. 0 to 50 mM).

2.5.2 According to the Examiner, the definitions of ionic strength and conductivity are unclear. In view of the above amendments to the claims, this objection should have been rendered moot.

3. AUXILIARY REQUESTS 1 TO 4

The arguments under items 2.2 to 2.5, above, apply, *mutatis mutandis*, to Auxiliary Requests 1 to 4.

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Moreover, Auxiliary Requests 1 to 4 are also novel over D3 by virtue of the molarity cited in step 1 of claim 1.

4. REQUESTS

With the above explanations and amendments to the Main Request and 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 and they should be cancelled. We request written confirmation in this regard.

As indicated in a telephone conversation with the first Examiner, Applicant is currently preparing additional data in support of the superior effect achieved by the method of the present invention.

Applicant will submit these data at his earliest convenience, one they have been obtained, in any event well in advance of the oral proceedings scheduled for April 19, 2016.

It is thus requested that the Examining Division will also consider these data still to be filed for the assessment of inventive step.

If, however, the Examining Division does not agree with the above, it is requested that a further Communication pursuant to Article 94(3) 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. Michaela Weße
European Patent Attorney

Encl.:
Main Request (marked-up and clean copy)
Auxiliary Requests 1 to 4 (marked-up and clean copies)

PFIZER, INC., IPR2017-01358, Ex. 1011, p. 33 of 60

D6

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.

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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**

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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

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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.

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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.

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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

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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

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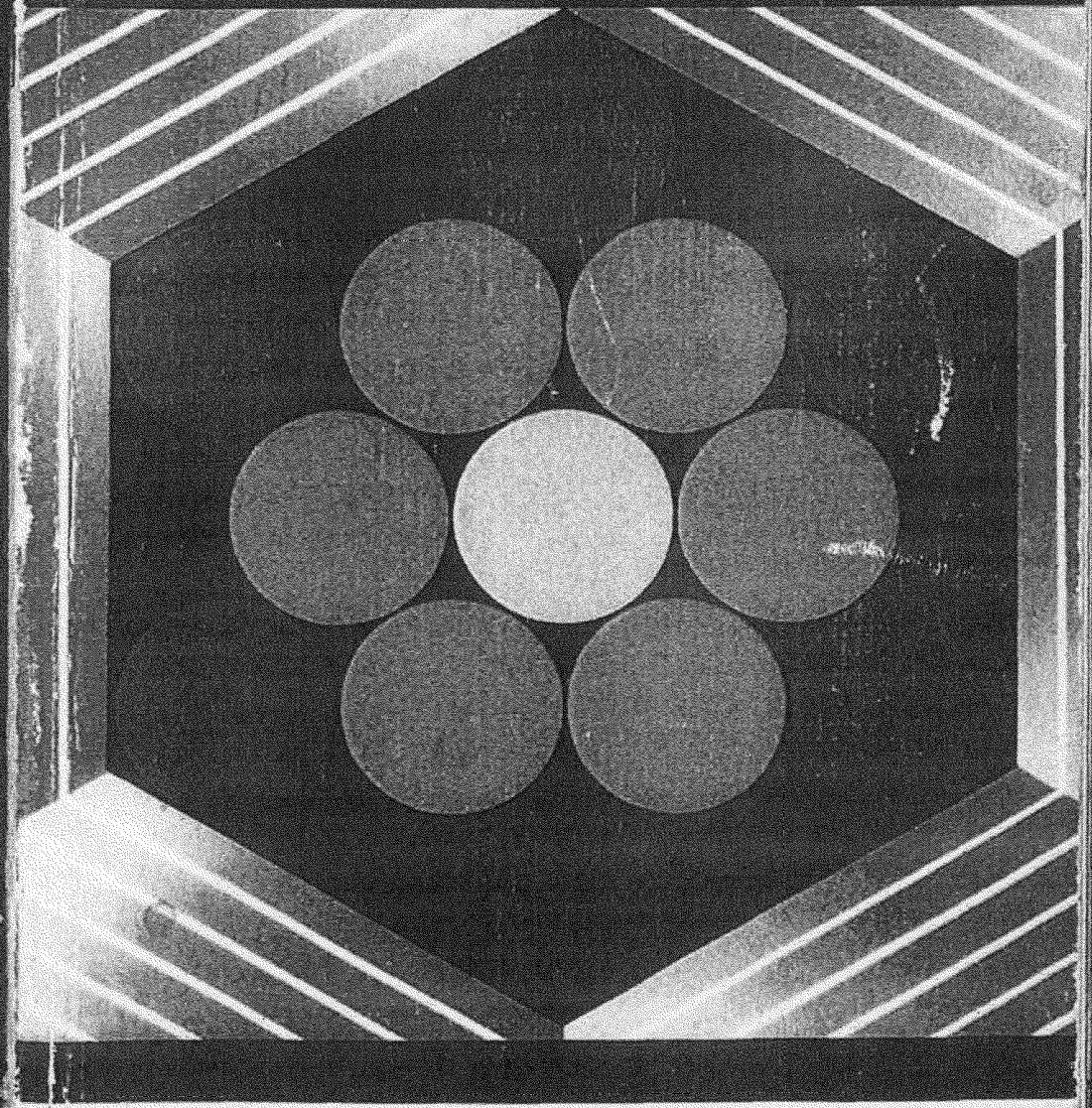
Physical Chemistry



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Second U.S. Edition (with answers to problems) published in Great Britain as Third Edition, 1957
New impressions 1958, 1959, 1960, 1961 and 1962
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In 1891, Stoney proposed that this natural unit of electricity should be given a special name, the *electron*.* Hence, 1 mol of electrons would equal 1 F of electric charge.

$$\mathrm{F} = Le \tag{10.2}$$

3. Coulometers

A careful measurement of the amount of chemical reaction caused by the passage of a certain amount of electric charge through an electrolytic cell gives a precise measure of the amount of electric charge that passed. Such a device for measuring charge passed is called a *coulometer*.

An example is the *silver coulometer*, which uses platinum electrodes in aqueous silver nitrate. The gain in mass of the cathode is measured after a current is passed through a solution of $AgNO_3$. The reaction at the cathode can be written

$$Ag^+ + e^- \longrightarrow Ag$$

One mole of silver, 107.870 g, is deposited on the cathode for each faraday passed through the coulometer. Thus, 1 C is equivalent to

$$\frac{107.870}{96\,487} = 1.118 \times 10^{-3} \text{ g of silver}$$

4. Conductivity Measurements

One of the earliest theoretical problems in electrochemistry was how solutions of electrolytes conducted an electric current.

Metallic conductors were known to obey Ohm's Law,

$$I = \frac{\Delta\Phi}{R} \tag{10.3}$$

where I is the current (amperes), $\Delta\Phi$ is the difference in electric potential between the terminals of the conductor (volts), and the proportionality constant R is the *resistance* (ohms). The resistance depends on the dimensions of the conductor. For a conductor of uniform cross section,

$$R = \frac{\rho l}{A} \tag{10.4}$$

Here, l is the length and A the cross-sectional area, and the specific resistance ρ ($\Omega \cdot$m) is called *resistivity*. The reciprocal of resistance is *conductance* (Ω^{-1}) and the reciprocal of resistivity is *specific conductance* or *conductivity* κ ($\Omega^{-1} \cdot m^{-1}$).

The first studies of the conductivity of solutions were made with rather large direct currents. The resulting electrochemical action was so great that erratic

*Later, an elementary particle was discovered with a charge of $-e$, and this particle was given the name *electron*. The unit of charge e is 1.6021×10^{-19} C, the charge of the proton.

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results were obtained, and it appeared that Ohm's Law was not obeyed—i.e., the conductivity seemed to depend on the $\Delta\Phi$. This result was largely due to *polarization* at the electrodes of the conductivity cell—i.e., a departure from equilibrium conditions in the surrounding electrolyte.

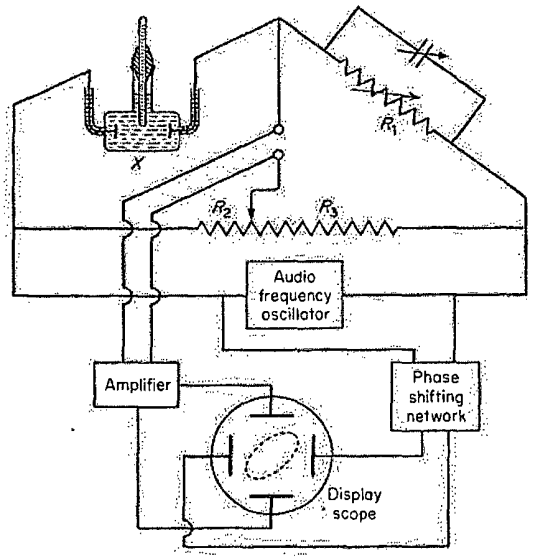

FIG. 10.1 AC Wheatstone bridge for measurement of conductance of electrolytes.

These difficulties were overcome by the use of an alternating-current (a-c) bridge, such as that shown in Fig. 10.1. With a-c frequencies in the audio range [1000 to 4000 hertz (Hz)], the direction of the current changes so rapidly that polarization effects are eliminated. One difficulty with the a-c bridge is that the cell acts as a capacitance in series with a resistance, so that even when the resistance arms are balanced there is a residual unbalance due to the capacitances. This effect can be partially overcome by inserting a variable capacitance in the other arm of the bridge, but for very precise work further refinements are necessary.*

The balance point of the bridge is indicated on the cathode-ray oscilloscope. The voltage from the bridge midpoint is filtered, amplified, and fed to the vertical plates of the oscilloscope. A small portion of the bridge input signal is fed to the horizontal plates through a suitable phase-shifting network. When the two signals are properly phased, the balance of capacitance is indicated by the closing of the

*T. Shedlovsky, *J. Am. Chem. Soc.*, *54*, 1411 (1932); W. F. Luder, *J. Am. Chem. Soc.*, *62*, 89 (1940); J. Braunstein and G. D. Robbins, *J. Chem. Ed.*, *48*, 52 (1971). The last authors analyze the sources of capacitance in a-c bridge measurements of electrolytic solutions and show that the principal capacitance is in series with the electrolyte and arises from the charging and discharging of the double layer at the surface of the electrodes. (See Section 11.19.)

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loop on the oscilloscope screen, and the balance of resistance is indicated by the tilt of the loop from horizontal.

A typical conductivity cell is also shown in Fig. 10.1. Instead of measuring their dimensions, we now usually calibrate these cells before use with a solution of known conductivity, such as one-molar potassium chloride. The cell must be well thermostatted, since conductivity increases with temperature.

As soon as reliable conductivity data were available, it became apparent that solutions of electrolytes followed Ohm's Law. Resistance was independent of potential difference,* and the smallest applied voltage sufficed to produce a current of electricity. Any conductivity theory would have to explain this fact: the electrolyte is always ready to conduct electricity, and this capability is not something produced by the applied electric field.

On this score, the ingenious theory proposed in 1805 by C. J. von Grotthuss must be judged inadequate. He supposed the molecules of electrolyte to be polar, with positive and negative ends. An applied field lined them up in a chain. Then the field caused the molecules at the end of the chain to dissociate, the free ions thus formed being discharged at the electrodes. Thereupon, there was an exchange of partners along the chain. Before further conduction could occur, each molecule had to rotate under the influence of the field to reform the original oriented chain. Despite its shortcomings, the Grotthuss theory was valuable in emphasizing the necessity of having free ions in the solution to explain the observed conductivity. We shall see later that a mechanism similar to that of Grotthuss actually occurs in some cases.

In 1857, Clausius proposed that especially energetic collisions between undissociated molecules in electrolytes maintained at equilibrium a small number of charged particles. These particles were believed to be responsible for the observed conductivity.

5. Molar Conductances

From 1869 to 1880, Friedrich Kohlrausch and his coworkers published a long series of careful conductivity investigations. The measurements were made over a range of temperatures, pressures, and concentrations.

Typical of this painstaking work was the extensive purification of the water used as a solvent. After 42 successive distillations *in vacuo*, they obtained a *conductivity water* with $\kappa = 4.3 \times 10^{-6}\ \Omega^{-1} \cdot m^{-1}$ at 18°C. Ordinary distilled water in equilibrium with the carbon dioxide of the air has a conductivity of about $70 \times 10^{-6}\ \Omega^{-1} \cdot m^{-1}$.

To reduce conductivities to a common concentration basis, a function called the *molar conductance* is defined by

$$\Lambda = \frac{\kappa}{c} \tag{10.5}$$

*At high electric field strengths, however, departures from Ohm's Law will be observed.

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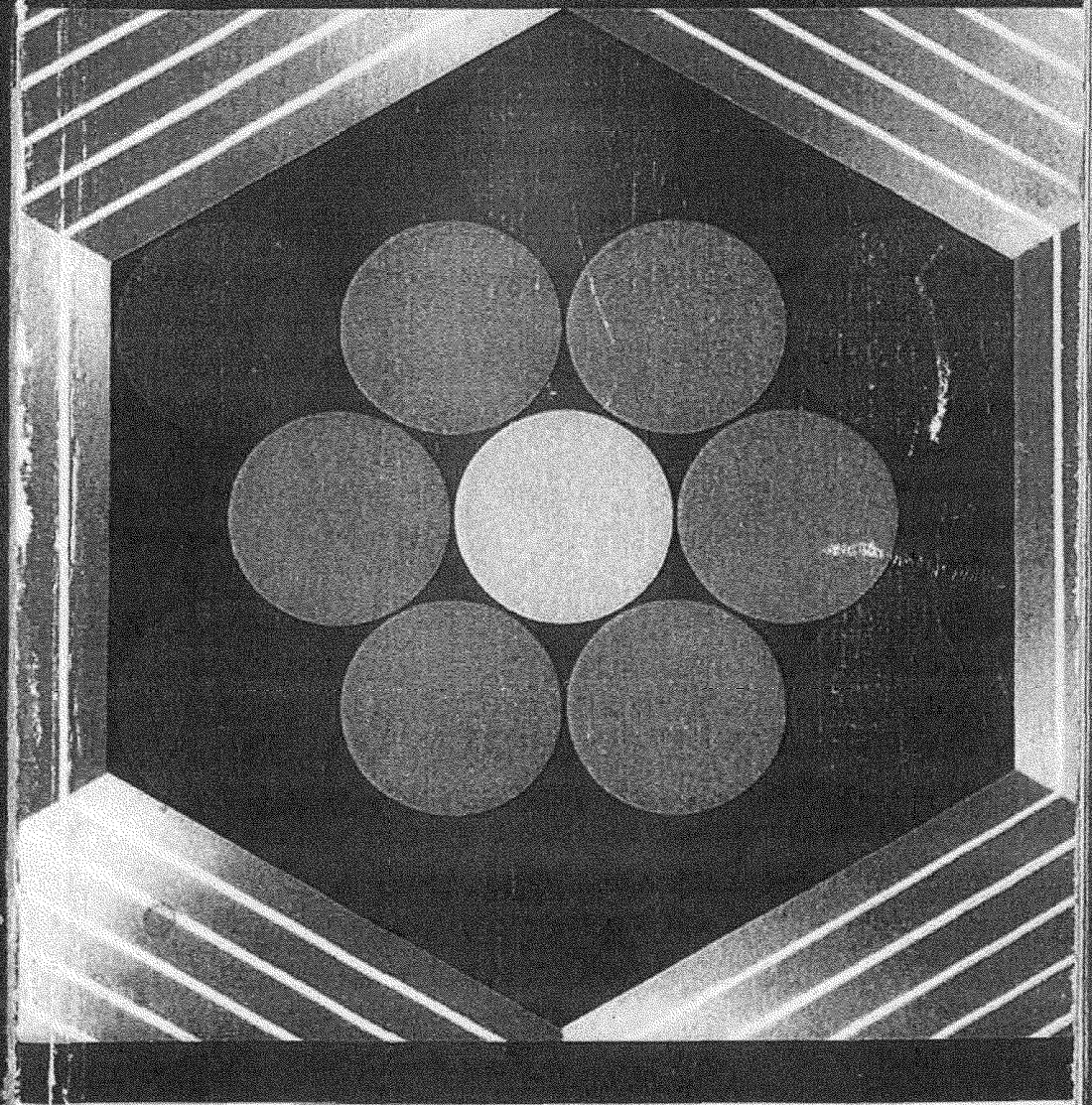
Physical Chemistry



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The integration in this expression can be carried out graphically from a series of measurements of the freezing point depression in solutions of known low concentrations. We plot j/m vs. m, extrapolate to zero concentration, and measure the area under the curve. A similar treatment is applicable to osmotic-pressure data.

18. The Ionic Strength

Many properties of ionic solutions depend on electrostatic interactions between ionic charges. The electrostatic force between a pair of doubly charged ions is four times the force between a pair carrying unit charges. A useful function of ionic concentration, devised to include such effects of ionic charge, is the ionic strength I, defined by

$$I = \tfrac{1}{2} \sum m_i z_i^2 \tag{10.32}$$

The summation is taken over all the different ions in a solution, multiplying the molality of each by the square of its charge.

For example, a 1.00 molal solution of NaCl would have an ionic strength $I = \frac{1}{2}(1.00) + \frac{1}{2}(1.00) = 1.00$. A 1.00 molal solution of $La_2(SO_4)_3$ would have

$$I = \tfrac{1}{2}[2(3)^2 + 3(2^2)] = 15.0$$

In dilute solutions, the activity coefficients of electrolytes, the solubilities of sparingly soluble salts, rates of ionic reactions, and other related properties become functions of ionic strength.

If the molar concentration c is used instead of the molality m,

$$c = \frac{m\rho}{1 + mM}$$

where ρ is the density of the solution and M is the molar mass of the solute. In dilute solution, this relation approaches $c = \rho_0 m$, where ρ_0 is the density of the solvent. Therefore,

$$I = \tfrac{1}{2} \sum m_i z_i^2 \approx \frac{1}{2\rho_0} \sum c_i z_i^2 \tag{10.33}$$

19. Experimental Activity Coefficients

Mean activity coefficients obtained by various methods* are summarized in Table 10.6 and plotted in Fig. 10.6. For comparison, the activity coefficient of a typical nonelectrolyte, sucrose, is also shown. Quite typically the coefficients for electrolytes decline markedly with increasing concentration in dilute solution, but then pass through minima and rise again in more concentrated solutions. The interpretation of this behavior constitutes one of the principal problems in the theory of strong electrolytes.

*An extensive tabulation was given by H. S. Harned and B. B. Owen, *The Physical Chemistry of Electrolytic Solutions* (New York: Reinhold Publishing Corp., 1950).

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D7

In the matter of European Patent Application No. 02703958.5 - 2405

Published as EP1380589

in the name of Chugai Seiyaku Kabushiki Kaisha

APPENDIX 1 - Ionic strength calculation for ProSep Elution Buffer of D3 (25mM citrate, pH 3.5)

Ionic strength

The ionic strength of a solution is a measure of the concentration of ions in that solution. Ionic compounds, when dissolved in water, dissociate into ions. The total electrolyte concentration in solution will affect important properties such as the dissociation or the solubility of different salts. One of the main characteristics of a solution with dissolved ions is the ionic strength.

The ionic strength, I, of a solution may be expressed as a function of the concentration of all ions present in that solution.

$$I = \frac{1}{2}\sum_{i=1}^{n} c_i z_i^2$$

where c_i is the molar concentration of ion i (M, mol/L), z_i is the charge number of that ion, and the sum is taken over all ions in the solution.

Calculation of molar ionic strength of elution buffer of D3

Elution buffer: 25 mM Citrate buffer, pH 3.5,

H_3citrate $\rightarrow H^+ + H_2$citrate$^-$, pK_{a1} for citrate = 3.13

H_2citrate $\rightarrow H^+ +$ Hcitrate^{2-}, pK_{a2} for citrate = 4.76

From the Henderson-Hasselbalch equation:

(1) $pH = pK_{a1} + \log([H_2A^-]/[H_3A])$

$pH - pK_{a1} = \log([H_2A^-]/[H_3A]) = 3.5 - 3.13 = 0.37$

Thus, $[H_2A^-]/[H_3A] = 10^{0.37} = 2.344$, **$[H_2A^-] = 2.344 \times [H_3A]$**

(2) $pH = pK_{a2} + \log([HA^{2-}]/[H_2A^-])$

$pH - pK_{a2} = \log([HA^{2-}]/[H_2A^-]) = 3.5 - 4.76 = -1.26$

Thus, $[HA^{2-}]/[H_2A^-] = 10^{-1.26} = 0.055$, **$[HA^{2-}] = 0.055 \times [H_2A^-] = 0.129 \times [H_3A]$**

Since the concentration of the citrate buffer is 0.025M:

$[H_3A] + [H_2A^-] + [HA^{2-}] = 0.025$,

$[H_3A] + 2.344 \times [H_3A] + 0.129 \times [H_3A] = 0.025$,

$3.473 \times [H_3A] = 0.025$,

Therefore,

$[H_3A] = 0.0072$ M, $[H_2A^-] = 0.0168$ M, $[HA^{2-}] = 0.00093$ M

The 3 ions $[H^+]$, $[H_2A^-]$ and $[HA^{2-}]$ (H_2citrate$^-$ ($C_6H_3O_7^-$) and Hcitrate^{2-}($C_6H_2O_7^{2-}$)) are present in the elution buffer.

Since the ionic strength of the elution buffer is:

$$I = \frac{1}{2}\sum_{i=1}^{n} c_i z_i^2$$

I = 1/2 × [(concentration of $[H^+]$ × (charge of $H^+)^2$ + concentration of $[H_2A^-]$ × (charge of $H_2A^-)^2$) + (concentration of $[H^+]$ × (charge of $H^+)^2$ + concentration of $[HA^{2-}]$ × (charge of $HA^{2-})^2$)]

I = 1/2 × [(0.0168 M × $(+1)^2$ + 0.0168 M × $(-1)^2$) + (2 × 0.00093 M × $(+1)^2$ + 0.00093 M × $(-2)^2$)]

I = 0.01959 M

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

Description, Pages

1, 2, 7, 8, 13, 15-29	as originally filed			
3-6, 9-12, 14	received on	22-10-2012	with letter of	19-10-2012

Claims, Numbers

1-9	received on	31-07-2013	with letter of	30-07-2013

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D3 WO 95/22389 A1

The following documents are cited by the Examiner. Copies of the documents are annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D6 Third party observations filed on 02.10.2015 in the proceedings of the parental application

D7 Annex to the Third party observations filed on 02.10.2015 in the proceedings of the parental application

1 Amendments (**Article 123 EPC**)

No basis can be found in the application as originally filed for the specific combination of features defining the acidic aqueous solution in claim 1, step 1). According thereto, the protein-containing sample is converted either into a) "*... an acidic aqueous solution of low conductivity of an ionic strength of 0.2 or less [...] and having a molarity of less than 50 mM and a pH of 1.5 to 3.9*" or into b) "*... an acidic aqueous solution of low conductivity of [....] a conductivity of 300 mS/m or less and having a molarity of less than 50 mM and a pH of 1.5 to 3.9*".

The applicant cited original claims 5 and 6 as well as pages 10-12 of the description as alleged basis.

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However, none of said passages discloses the combination of a specific molarity with either a specific ionic strength or a specific conductivity. In contrast, the features of original claims 4-6 (specific molarity, specific ionic strength and specific conductivity, respectively) are clearly formulated as alternatives and not as a combination.

The passage on page 11, lines 12-20, of the description defines the acidic aqueous solution of low conductivity as "*... an aqueous solution of pH 1.5 to pH 3.9 [...] which has a molarity of 0 to 100 mM [...] or has a ionic strength of 0 to 0.2 [...] or has a conductivity of 0 to 300 mS/m [...]*". Again, the features of molarity, ionic strength and conductivity are formulated as alternatives.

Even if the ranges selected in claim 1.1) for ionic strength, conductivity or molarity are present as possible alternatives in said passage of the description, the specific selection of features referred to in claim 1.1) is not disclosed in the application as originally filed.

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).

2 Novelty (**Article 54 EPC**)

Third party observations D6 were filed on 02.10.2015 in the proceedings of the parental application. The argumentation in said third party observations as to lack of novelty in view of D3 also applies *mutatis mutandis* to the present claims.

Example IA of D3 describes the conversion of a sample containing the humanized monoclonal antibody RSHZ-19 into an acidic aqueous solution of low conductivity, i.e. into an eluate comprising 25 mM citrate and having a pH of 3.5. The eluate is then readjusted to pH 5.5 by addition of TRIS buffer and filter through a prefilter and a 0.2 µm filter (D3, e.g. page 14, line 10 - page 15, line 2; table 1; page 19, lines 4-20). As calculated in D7, the elution buffer of D3 exhibits an ionic strength of 0.01959 M and a conductivity at 25°C of around 150 mS/m.

Consequently, D3 is novelty-destroying for claims 1-7 and 9, even if D3 does not explicitly refer to a method for removing contaminant DNA in a sample.

However, where a claim is directed to a method aiming at a certain purpose and comprises physical steps which result in the production of a product, the indication of the intended purpose of the method is to be understood in the sense that the method has to be merely suitable for that use. Consequently, a

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prior disclosure of the same method without an explicit indication of the particular purpose, although the method is nevertheless suitable for it, would anticipate a claim to the method for that particular purpose (**Guidelines, F-IV, 4.13; T304/08, T1039/09; T428/09**).

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

The objection is maintained in its entirety that the problem has not been solved over the whole scope of the claims for the reasons already outlined in the previous communications and in the following:

The Examining Division has serious doubts, that all methods falling under the scope of the claims actually remove contaminant DNA from a protein-containing sample. Negative examples are already given in the present application disclosing that e.g. adjusting the pH of the eluate to pH 4.0 does not result in removal of contaminating DNA (description, e.g. example 2, table 3, pH4.0 vs pH 2.7). Since such negative examples do not solve the technical problem, they cannot be considered as being inventive (**Article 56 EPC**).

The present claims are merely an invitation to start a research project. Only specific conditions will lead to success. For example, it is not credible that the acidic aqueous solution is adjusted to a pH of 4 to 8 but has nevertheless a molarity of e.g. 0 mM. It is also not credible that a solution with 0 mM molarity results in precipitation of DNA contaminations but not in precipitation of the protein of interest. 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.

Since the problem has not been solved over the whole scope, claims 1-9 do not meet the requirements of **Article 56 EPC**.

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

4.1 The objection is maintained in its entirety that there are serious doubts that the method works over the whole claimed range. For example, it is not credible that DNA contaminants will precipitate in an aqueous solution of e.g. 0 mM molarity, i.e. without any salt, while the protein of interest will remain in solution. For an aqueous solution of 0 M molarity it is e.g. also not possible to adjust the required pH of 4 to 8.

4.2 None of the examples discloses a method as claimed.

Examples 1-3 disclose the pH and the molarity of the acidic aqueous solution into which the protein-containing sample is converted but the examples are silent with respect to conductivity or ionic strength of said acidic aqueous solution. Said parameters are neither directly nor indirectly unambiguously

derivable. Also not disclosed in the examples is the amount of residual DNA, e.g. in pg/ml which is observed after performing the method. It is therefore not possible to determine clearly and unambiguously to what extent contaminant DNA was removed in the examples.

Examples 4-6 only disclose in general that a protein-containing sample is diluted in 2.5 mM aqueous HCl and further converted into an acidic aqueous solution of low conductivity using 20% hydrochloric acid. Neither the volumes, the pH, the conductivity, the ionic strength or the molarity of the converted samples is disclosed let alone the results of DNA assays after pH adjustment and filtration. Examples 4-6 are therefore not suited to as basis for the present claims.

Claim 1 extends to any method comprising a conversion of the protein-containing sample into any "*... acidic aqueous solution of low conductivity of a ionic strength of 0.2 or less or a conductivity of 300 mS/m or less and having a molarity of less than 50 mM and a pH of 1.5 to 3.9*". Such methods have not been shown in the application. It would require undue burden for the skilled person to test each and every acidic aqueous solution falling under the definition in the claims whether it has the desired activity.

Moreover, it is not reasonable to extrapolate the teaching of the specific methods disclosed in the examples to all methods covered by the claims. The description itself discloses that adjusting the acidic aqueous protein-containing solution to pH 4.0 does not achieve the effect of removing contaminant DNA (description, e.g. example 2, table 3, pH 4.0 vs pH 2.7). Such a method is however considered as being covered by the claims.

Therefore, claims 1-9 are not enabled over the whole scope of the claims and also not technically supported by the description as their scope is broader than justified by the description and drawings. The scope of the claims should be restricted such that it is commensurate with the teaching of the application.

4.3 A further lack of sufficiency of disclosure arises from the unclear definition of parameters in claim 1.1).

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.

5 Clarity (**Article 84 EPC**)

5.1 The objections as to lack of clarity are maintained in its entirety for the reasons outlined in the previous communications

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Briefly, it is not clear to which compound(s) the parameter "*... molarity of less than 50 mM...* " in claim 1.1) refers to and the nature of the acidic aqueous solution to be used in claim 1.1) is open to interpretation.

5.2 The definition of the parameters "*ionic strength*" and "*conductivity*" in claim 1.1) is unclear for the reasons outlined in D6.

Briefly, no units are provided for the ionic strength and it is not indicated at which temperature the conductivity must be measured. Therefore, said parameters are open to interpretation.

6 At least some of the objections raised above, in particular the objections under **Articles 123, 56** and **83/84 EPC**, are such that there appears to be no possibility of overcoming them by amendment. A refusal of the application under **Article 97(2) EPC** has to be expected.

Since the Applicant has requested oral proceedings in the case of an unfavourable decision, herewith oral proceedings according to **Rule 115 EPC** are summoned. During these oral proceedings the above mentioned objections will be discussed.

Should the applicant intend to present new claims, he/she is invited to file such claims before the final date for written submissions and/or amendments which is indicated on the summons to oral proceedings. The applicant is informed that the examining division will not accept late filed claims (**Rule 116 EPC**).

Further amendments of the claims will be admitted according to **Rule 137(3) EPC** only if said amendments are suitable to overcome the objections made above and if said amendments do not create additional objections.

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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Application No.: 10 011 215.0

Preparation for oral proceedings - Instructions to Support Service

Oral proceedings are to be held in connection with the above patent application

1. The matters to be discussed are set out in the annex (Form 2906)

2. Dispatch the summons using Form 2008/2310 and Form 2906 for the parties to attend on:

Day 19.04.2016 Time 09:00

ROOMS

Provisionally in 1st examiner's room.

9999

Room booked

ORAL 01, 02, 03 and 05 coded

ST 14.10.15

Date Initials

2.1 Parties' submissions in preparation for the oral proceedings, if any, should be made no later than

1 month(s)

before the date of the oral proceedings
(transfer to Form 2008.1 / 2310.1)

2.2 Encode ORAL(04) coded

ST 14.10.15

Date Initials

2.3 Dispatch Form 2008.7 / 2310.7 to division

ST 14.10.15

Date Initials

3. ☐ Arrange for the following special equipment to be provided in the conference room:

Date Initials

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Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

4. Request language service to provide simultaneous interpretation facilities as necessary

Date Initials

5. Return the dossier to primary examiner with Form 2041 (15 days before the oral proceedings)

Date Initials

6. Check that summons has been received (Form 2936 / advice of delivery)

7. 15 days before the oral proceedings:
- dispatch the dossier to the primary examiner.

07.10.2015
Date

Stoyanov, Borislav	Rojo Romeo, Elena	Sommer, Birgit	
Chairman	2nd examiner	1st examiner	Legal member

Enclosure(s):
D6, D7

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GERMANY

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

Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München
ALLEMAGNE

Date: 19-10-2015

Reference	Application No./Patent No.
H2624 EP/1 S3	10011215.0 - 1410 / 2336149

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 19.04.16 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 18.03.16.

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	Rojo Romeo E	Stoyanov B

For the Examining Division

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

Registered letter with advice of delivery to EPO postal service: 14.10.15

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VOSSIUS & PARTNER
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EP 10 01 1215.0
Chugai Seiyaku Kabushiki Kaisha
Our Ref.: H2624 EP/1 S3

30. Juli 2013

AMENDED CLAIMS SET

1. A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the following steps:
   1) converting the sample containing a physiologically active protein into 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 ~~0 to 100~~**less than 50** mM and a pH of 1.5 to 3.9;
   2) adjusting the pH of the resulting sample to a pH of 4 to 8; and
   3) removing the resulting particles.

~~2. The method according to claim1, wherein the acidic aqueous solution of low conductivity has an ionic strength of 0 to 0.2.~~

~~3. The method according to claim 1, wherein the acidic aqueous solution of low conductivity has a conductivity of 0 to 300 mS/m.~~

~~4~~2. The method according to ~~any one of~~ claims ~~1 to 3~~, wherein the acidic aqueous solution is selected from aqueous solutions of hydrochloric acid, citric acid and acetic acid.

~~5~~3. The method according to ~~any one of~~ claims ~~1 to 4~~**or 2**, wherein the contaminant DNA is present at a DNA concentration of 22.5 pg/ml or less in the treated sample containing a physiologically active protein.

~~6~~4. The method according to claim 1, wherein an aqueous solution of Tris is used to adjust the pH of the resulting sample.

~~7~~5. The method according to claim 1, wherein the pH of the resulting sample is adjusted to

pH of 4.3 to 7.5.

86. The method according to claim 1, wherein the physiologically active protein is an antibody.

97. The method according to claim 86, wherein the antibody is a humanized monoclonal antibody.

108. The method according to claim 97, wherein the antibody is a humanized anti-IL-6 receptor antibody.

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