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Datasheet for the decision of 21 November 2014

Case Number: T 0047/10 - 3.3.06

Application Number: 97923962.1

Publication Number: 0907378

IPC: A61K39/395, C07K16/28

Language of the proceedings: EN

Title of invention:
Method for the concentration of antibody solutions

Patent Proprietor:
GLAXO GROUP LIMITED

Opponent:
Bayer Pharma Aktiengesellschaft

Headword:
Concentration of antibodies/GLAXO

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Amendments - added subject-matter (yes)

Decisions cited:

Catchword:

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Beschwerdekammern
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Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0047/10 - 3.3.06

D E C I S I O N
of Technical Board of Appeal 3.3.06
of 21 November 2014

Appellant: (Opponent)	Bayer Pharma Aktiengesellschaft Müllerstrasse 178 13353 Berlin (DE)
Representative:	Weiss, Wolfgang Weickmann & Weickmann Patentanwälte Postfach 86 08 20 81635 München (DE)
Respondent: (Patent Proprietor)	GLAXO GROUP LIMITED Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB)
Representative:	Hitchcock, Lucy Rose GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 October 2009 rejecting the opposition filed against European patent No. 0907378 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	B. Czech
Members:	E. Bendl
	U. Lokys

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division to reject the opposition against the European patent no. 0 907 378.

II. Independent process claim 15 of the application as filed (published as WO 97/45140 A1 under the PCT) reads as follows:

"*15. A process for the preparation of a monoclonal antibody preparation in which the antibody in said preparation is at a concentration of 100 mg/ml or greater by tangential flow ultrafiltration.*"

III. Independent process claim 1 of the patent as granted reads as follows:

"*1. A process for concentrating an antibody preparation which process comprises the steps of;*

(a) Subjecting an antibody preparation to cross flow ultra filtration with a recirculation rate of 250 ml/min wherein said antibody preparation is filtered through a 30K membrane.

(b) *Recovering a final antibody preparation of step (a).*"

IV. In its statement setting out the grounds of appeal the appellant (opponent) *inter alia* held that the requirements of Articles 123(2) EPC were not met by the claimed subject-matter of the patent-in-suit.

V. With its reply of 1 September 2010 the respondent (patent proprietor) rebutted the appellant's

objections, filed two sets of amended claims as main and auxiliary request and held, that these claims met the requirements of the EPC.

VI. In a communication issued with the summons for oral proceedings the board asked for clarification with regard to the pending requests of the respondent and called into question whether the claims at issue met the requirements of Article 123(2) EPC.

VII. In response thereto, the respondent submitted with its letter dated 24 September 2014 a main request (claims as granted) and a set of amended claims as auxiliary request, said requests replacing the ones previously on file.

The wording of claim 1 of the auxiliary request differs from the wording of claim 1 of the main request (point III, supra) in that feature "*wherein the antibody is IgG*" is appended to the latter.

VIII. With its letter of 29 October 2014 the respondent withdrew its pending request for oral proceedings and announced that it would not attend the oral proceedings already scheduled.

IX. Thus, oral proceedings took place on 21 November 2014 in the absence of the respondent. The only issue discussed was whether the respective claims according to the two requests on file met the requirement of Article 123(2) EPC.

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

The respondent requested in writing that the patent be

maintained on the basis of the main request (claims as granted), i.e. that the appeal be dismissed, or, alternatively, that the patent be maintained on the basis of the claims according to the auxiliary request filed with its letter of 24 September 2014.

XI. The appellant's arguments of relevance here can be summarised as follows:

Allowability of the amendments (Article 123(2) EPC)

Main request

- The combination of features of claim 1 was not originally disclosed.
- The passage on page 7 as originally filed, referred to by the respondent, related to the recirculation rate of 250 ml/min only in combination with a concentration of antibody > 150 mg/ml and did not describe the use of a "*30K*" membrane, i.e. of a membrane with a molecular weight cutoff value of 30 kDa (kilo dalton).
- Example 3 of the original application related to the concentration of a specific antibody, using a specific filtration system ("Filtron Mini-Ultrasette") and achieving a maximum concentration of approximately 150 mg/ml. The teaching of this example could not be generalised.
- The concentration of the "*final antibody preparation*" obtained was not defined in claim 1. The one defined in claim 2 was not originally disclosed.
- Thus, claims 1 and 2 of the patent as granted did not meet the requirement of Article 123(2) EPC.

Auxiliary request

- The reasoning given with regard to the claims of

the main request applied also to the amended claims 1 and 2 of the auxiliary request.

The respondent's arguments of relevance here can be summarised as follows:

Allowability of the amendments (Article 123(2) EPC)

Main request

- The application as filed disclosed on page 7, lines 23 to 27 a method for concentrating an antibody preparation with reduced shear stress on the preparation, achieved by means of a circulation rate decreased from high values (500 ml/min) to lower values, as for instance 250 ml/min, which method led to "*successful concentration of antibody > 150 mg/ml*".
- As the concentration of the antibody preparation only expressed a result achievable by performing the disclosed method, the omission, in claim 1 as granted, of a minimum concentration value complied with the requirement of Article 123(2) EPC.
- A 30 kDa membrane was used in each of the examples of the patent-in-suit, 30 kDa being the standard cutoff value known to be suitable for antibody concentration/separation. The skilled person would understand that this cutoff size "was a feature of the invention".
- Antibodies/Fab fragments as referred to in the patent in suit had a size from 55 to 900 kDa and could therefore be separated by a 30 kDa membrane. Also according to document D4 (Cytotechnology 16, 79-87, 1994) a 30 kDa membrane was used for concentrating an IgG antibody. A 30 kDa membrane was not "specific to an anti-CD4 antibody". The teaching of example 3 and of the patent in

general was thus not limited to the concentration of anti-CD4 antibodies, the latter only represented a specific embodiment.

- Although a Filtron Mini-Ultrasette was used in the examples of the patent-in-suit, any other filter system could be used instead.
- Therefore, the subject-matter of the claims met the requirement of Article 123(2) EPC.

Auxiliary request

- In claim 1 of this request, the type of antibody to be concentrated, i.e. IgG, was defined more precisely compared to claim 1 of the main request. The concentration of IgG being disclosed as a preferred embodiment on page 4, lines 26 to 28 of the application as filed, this set of claims met the requirement of Article 123(2) EPC too.

Reasons for the Decision

Allowability of the amendments - Article 123(2) EPC

1. Main request

1.1 Whereas the appellant held that the combination of features defining the subject-matter of claim 1 as granted (see III, *supra*) was not disclosed in the application as filed, the respondent considered that claim 1 as granted found basis in two parts of the application as filed, namely in the third full paragraph on page 7 and in example 3 (page 15, penultimate paragraph).

1.2 The board does not accept that the amendments made to process claim 15 as originally filed, which resulted in

claim 1 as granted, find basis in the application as filed for the following reasons:

1.2.1 The paragraph on page 7 refers to a method of concentrating antibodies by means of a cross-flow ultrafiltration at a circulation rate lower than 500 ml/min. It is expressly stated that "*reducing the recirculation to for example 250 ml/min leads to successful concentrations of antibody to* ***> 150*** *mg/ml and the to* ***high recovery*** *of material*" (emphasis added by the board).

1.2.2 For the board, said particular paragraph does not provide a sufficient basis for the amendments resulting in claim 1 at issue for at least two reasons:

(a) No reference is made to the cutoff value of the membrane to be used. The board does not accept the argument of the respondent that a 30 kDa membrane represented the standard membrane known to the skilled person to be suitable for the concentration of all kinds of antibodies: for instance, document D4, referred to by the respondent to corroborate its allegation, describes the use of two different membranes for the concentration of an IgG, namely of a 100 kDa membrane and of a 30 kDa membrane, and recommends to investigate the suitability of membranes with an intermediate cutoff value (see page 85, right-hand column, lines 10 to 35).

In view of these indications in D4, the board is not convinced that 30 kDa membranes are to be considered as "the" standard membranes to be used in concentrating any any kind of antibody by cross-flow ultrafiltration, as apparently held by

the respondent.

In the application as filed, the cutoff size of the membrane used is only mentioned in the three examples describing ultrafiltration ("*30K*" in each case), out of which two (examples 1 and 2) do not describe a process falling within the terms of claim 1 as granted, since the recirculation rates mentioned (600 ml/min and 190 ml/min) differ from the one required by claim 1 (250 ml/min).

For the board, given that antibodies may have quite different molecular weights (see point XI, *supra*), the fact that a single example (example 3) mentions the specific membrane cutoff value of "*30K*" does not imply, absent any further explanation in the description as to why this specific combination of cutoff size of the membrane and recirculation rate of 250 ml/min should necessarily be applicable to all crossflow ultrafiltration processes conceivable upon reading the application, irrespective of the kind of antibody to be concentrated and the apparatus and/or process conditions used.

Hence, the board concludes that in the light of the whole content of the application as filed, the use of a "*30K*" membrane cannot be seen as a generic teaching to always use a membrane with precisely this cutoff value in the context of all processes falling within the terms of claim 1.

(b) As regards the basis for amendment to be provided by paragraph on page 7, the board notes that it refers to the concentration of antibodies to **more than** 150 mg/ml. In contrast thereto, the wording

of claim 1 comprises no numerical limitation in this respect. Only according to claim 2 as granted "*the **final** antibody preparation is > 150 mg/ml*" (emphasis added by the board).

This means that even processes leading to a low final antibody concentration of the preparation (e.g. below 100 mg/ml) are encompassed by the wording of claim 1. However, such a process is neither disclosed on page 7 nor anywhere else in the application as filed. Throughout the application as filed, it is repeatedly emphasised, and hence presented as an essential feature, that the antibody **preparations** according to the invention are supposed to have a **minimum** concentration of antibody of **at least 100** mg/ml. In this respect, reference is made to independent claims 1 and 14 to 16; page 3, lines 1 to 3 and lines 24 to 27 ; and page 4, lines 9 to 13.

Hence, the respondent's argument that the concentration of the antibody achieved would only be the result of the method applied, and could be omitted from the wording of independent process claim 1, is not accepted by the board.

1.2.3 From the above, the board concludes that said paragraph on page 7 does not directly and unambiguously disclose the subject-matter defined by the combination of features of claim 1 as granted.

1.3 With regard to the second part of the application as filed allegedly providing the basis for a process with all the features of claim 1 as granted, i.e. example 3, the board observes, that this example specifically describes the concentration of an anti-CD4 antibody by

means of a Filtron Mini-Ultrasette ultrafiltration device.

1.3.1 In its reply of 17 June 2010 the respondent implicitly acknowledged that several parameters, other than the recirculation rate and the membrane cutoff size, may have an influence on the concentration process and on the shear stress applied to the antibodies to be concentrated. For instance, it conceded that the skilled person "knows that there are other parameters which will have some effect on the concentration process, but he knows that these can vary, whilst the size of the membrane and flow rate through said membrane cannot vary" (page 5, paragraph 5.2; page 6, first sentence) and that "by increasing the cross-sectional filtration area the shear stress exerted would decrease further" (page 6, paragraph 5.4).

1.3.2 As convincingly put forward by the appellant, the shear stress imposed on the antibodies during their filtration/concentrating will not only depend on the overall recirculation rate of the preparation, but also on the dimensioning (cross sectional area/diameter) of the retentate flow channel(s). Thus, given the fact that example 3 merely describes a single experiment carried out under specific conditions including a fixed recirculation rate and (implicitly) a fixed cross-sectional filtration area, as defined by the specific filtration apparatus used ("*Filtron Mini-Ultrasette*"), comprising specifically a 30 kDa membrane, whereas only the the recirculation rate of 250 ml/min and the cutoff value of 30 kDa are defined in claim 1, the board concludes that example 3 describes **specific results** obtained by concentrating a **specific antibody** (anti-CD4) under **specific conditions**, i.e. making use of a

Filtron Mini-Ultrasette in combination with a 30 kDa membrane and a recirculation rate of 250 ml/min.

1.3.3 Claim 1 as granted is not, however, limited to the use of a specific filtration device dimensioned and being operated such that the shear stress on the circulating preparation is necessarily the same and as low as the one implied by example 3. A circulation rate of 250 ml/min may, in a different device, lead to a significantly higher or lower shear stress.

Hence, in the board's judgement, a generalisation of the disclosure of example 3 resulting in the subject-matter defined by claim 1 as granted is not justified, even when considering the whole disclosure of the application as filed, including said paragraph on page 7.

1.3.4 In addition, as pointed out by the appellant, example 3 describes the use of a 30 kDa cutoff cross-flow ultrafilter membrane, a retentate recirculation of 250 ml/min and results which suggest that a reduction of the retentate flux (page 15, third paragraph) "*may provide a method for concentrating anti-CD4 to ~ 150 mg/ml by cross flow ultrafiltration*", i.e. to **approximately** 150 mg/ml.

In this connection, it was also pointed out by the appellant that it can be gathered from the description of the application as filed, and in particular from example 3 relied upon by the respondent, that the numerical values reported for the concentration of the antibody in the preparation indicate either a "*maximum*" concentration achieved in the concentration step by means of cross-flow ultrafiltration or a "***final***" concentration (see page 16, last paragraph and the two

first data rows in table 4).

1.3.5 For the board, it appears that in the light of these indications on page 16, the value of *~ 150 mg/ml* mentioned in said third paragraph of page 15 can be understood to refer to the **maximum** concentrations (table 4: 169 and 156 mg/ml) achieved in the two ultrafiltration runs described in example 3, whereas in contrast thereto, the **final** concentrations of the product of "*~ 100 mg/ml*" (table 4: 106,4 and 100,5 mg/ml) mentioned in the last paragraph of page 16 are expressly stated to be "*a result of dilution with the washes required to maximise the **recovery** from the ultrafiltration apparatus*" (emphasis added by the board).

1.3.6 Hence, in the board's judgement, example 3 discloses **specific values** of the concentration of **final** antibody preparations **recovered** which are only slightly higher than 100 mg/ml, obtained by applying specific conditions. In particular, example 3 does not directly and unambiguously describe "***recovering** a **final** antibody preparation*" with a concentration "*> 150 mg/ml*" as required by the process of claim 2.

1.3.7 In summary, example 3 does not provide the necessary basis for the subject-matter defined in claims 1 and 2 as granted.

1.4 Even taking into account the entire disclosure of the application as filed, none of the two passages invoked by the respondent discloses directly and unambiguously the totality of the subject-matter defined by claims 1 and 2 as granted. This subject-matter thus extends beyond the content of the application as filed.

1.5 Since, therefore, the requirement of Article 123(2) EPC is not met, the respondent's main request is not allowable.

2. Auxiliary request

2.1 The wording of claim 1 of the auxiliary request (VII, *supra*) differs from the wording of claim 1 of the main request only in that the antibody to be concentrated is defined more specifically to be "*IgG*".

2.2 Despite this limitation, claim 1 at issue relates to concentrating antibodies from the broad class of IgGs, and not to a specific antibody such as anti-CD4 antibody used in example 3.

The process according to claim 1 at issue thus still represents an generalisation of the process disclosed in example 3, also in respect of the antibody to be concentrated.

2.3 Since, for the board, the addition of said limiting feature has no bearing on the above reasoning regarding claims 1 and 2 according to the main request, it applies *mutatis mutandis* to claims 1 and 2 according to the auxiliary request.

2.4 Since, consequently, claims 1 and 2 of the auxiliary request do not meet the requirement of Article 123(2) EPC either, the respondent's auxiliary request is not allowable either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

D. Magliano B. Czech

Decision electronically authenticated