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Datasheet for the decision of 5 May 2022

Case Number: T 0462/21 - 3.3.02

Application Number: 10009914.2

Publication Number: 2292636

IPC: C07K1/34

Language of the proceedings: EN

Title of invention:
Process for concentration of antibodies and therapeutic products thereof

Applicant:
Genentech, Inc.
Novartis AG

Headword:

Relevant legal provisions:
RPBA 2020 Art. 13(2)
EPC Art. 56, 123(2)

Keyword:
Amendment of the case after summons
Amendments
Inventive step

Decisions cited:

Catchword:

Europäisches Patentamt
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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0462/21 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 5 May 2022

Appellant: (Applicant 1)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 (US)
Appellant: (Applicant 2)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 5 February 2021 refusing European patent application No. 10009914.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	S. Bertrand
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the applicants ("appellants") lies from the decision of the examining division to refuse European patent application No. 10 009 914.2 on the basis of the main request and auxiliary requests 1 and 2, all filed during oral proceedings. The current application is a divisional application of the parent application EP 05 806 393.4.

II. The following documents are referred to in the present decision:

D5 US 5 177 194 A

D6 M.H. Desai, Methods in Biotechnology, Downstream Processing of Proteins, 23-34

III. In its decision, the examining division concluded that the subject-matter of claim 1 of each of the main request and auxiliary requests 1 to 2 did not involve an inventive step in view of D5 as the closest prior art.

IV. In its statement setting out the grounds of appeal, the appellants contested the examining division's decision. It submitted claim sets for the main request and auxiliary requests 1 to 7. The appellants requested acceleration of the appeal proceedings.

V. In a communication, the board granted the appellants' request for acceleration of the appeal proceedings.

VI. The board issued a communication pursuant to Article 15(1) RPBA 2020 in preparation for the oral proceedings

scheduled according to the appellants' request. Objections under Articles 56, 84 and 123(2) and Rule 49(10) EPC were raised

VII. With a further letter dated 27 April 2022, the appellants submitted new claim sets according to the main request and the first to fourth auxiliary requests.

VIII. Oral proceedings before the board were held on 5 May 2022 by videoconference. During these oral proceedings, the appellants withdrew their main request and first auxiliary request and made their second auxiliary request filed with the letter dated 27 April 2022 their main request.

IX. The relevant appellants' request was that the decision under appeal be set aside and that the application be remitted for grant on the basis of the claims of the main request filed as the second auxiliary request by letter dated 27 April 2022.

X. The appellants' case relevant to the present decision may be summarised as follows.

Main request - admittance

- The main request was filed in response to the board's formal objections raised in the communication under Article 15(1) RPBA 2020. These objections had not been raised by the examining division. The request should thus be admitted.

Main request - added-matter

- Examples 5 and 6 were a pointer to combine the disclosure of the process conditions on page 10 with the temperature conditions on page 11 and to limit this process to the rhuMAb E25 antibody.

Main request - inventive step

- D5 was the closest prior art and disclosed a process for purifying an immunoglobulin fraction from a crude plasma protein fraction.

- The distinguishing feature was at least that each of steps a), b) and c) according to claim 1 was carried out at a temperature of 45±5 °C.

- The data in the application as filed showed that carrying out each of steps a), b) and c) according to claim 1 of the main request at a temperature of 45°C improved the yield and the concentration of rhuMAb E25 in comparison with a process in which each of steps a), b) and c) was carried out at room temperature.

- The technical problem in view of D5 was the provision of an improved process.

- Obviousness:

  - The purpose of D5 was to purify the immune serum globulin fraction from plasma and not monoclonal antibodies produced *in vitro* like rhuMAb E25 as required by claim 1 of the main request.

- D6 might imply that reduced viscosity and increased flux could decrease the duration of a filtration step, but there was no reason to expect an additional and advantageous effect on yield and concentration.

Reasons for the Decision

Main request

1. Admittance

The main request corresponds to the second auxiliary request filed on 27 April 2022, i.e. after the date the summons to oral proceedings was issued.

This main request (previous second auxiliary request) resulted from former auxiliary request 7 filed with the statement of grounds of appeal by way of amendment. The claims of the main request are identical to the claims of this auxiliary request 7 except that the terms "highly" and "about" were deleted in the claims, claim 3 was reformulated without changing the content, claims 13, 14, 16-19, 23, 24, 28, 29 and 31 were deleted, and SI-units were added in claims 17-19. These amendments represent an amendment of the appellant's appeal case made after issue of the summons.

2. In line with Article 13(2) RPBA 2020, any such amendment must, as a rule, not be taken into account unless there are exceptional circumstances justified with cogent reasons by the party concerned.

3. In the communication under Article 15(1) RPBA 2020, an objection of added-matter for claims 13, 14, 23, 24 and 31 of auxiliary request 7 then on file and an objection

of lack of clarity were raised (point 34.2 of the communication). The appellants filed the main request on 27 April 2022 and submitted that the main request dealt with the board's formal objections raised in the communication under Article 15(1) RPBA 2020. These formal objections had not been raised by the examining division, so the appellants had no reason to make these amendments earlier in the proceedings.

The board agrees that the new objections raised in the board's communication represent, within the meaning of Article 13(2) RPBA 2020, exceptional circumstances justifying the late filing of the main request.

For this reason, the board decided to admit the main request filed into the appeal proceedings.

4. Article 123(2) EPC

Claim 1 of the main request reads as follows:
"*1. A process for preparing ~~highly~~ concentrated ~~protein~~ **recombinant humanized anti-IgE antibody** compositions, comprising:*

*a) a first ultrafiltering of a first antibody preparation **having a concentration of 0.1 to 10 grams per liter** to provide a second ~~protein~~ **antibody** preparation **as the retentate, wherein the second antibody preparation has a concentration of 10 to 50 gras per liter;***
*b) a diafiltering of the second antibody preparation to provide a diafiltered intermediate ~~protein~~ **antibody** preparation as the retentate, **wherein the diafiltered intermediate antibody preparation has the same concentration as the second antibody preparation;** and*

c) a second ultrafiltering of the diafiltered intermediate ~~protein~~ ***antibody*** *preparation to provide a third antibody preparation* ***as the retentate of the second ultrafiltration, wherein the third antibody preparation has a concentration of 150 to 200 grams per liter;***

wherein ~~one or more of the first ultrafiltering, second ultrafiltering, and the diafiltering are accomplished at about 30"°C to about 50°C~~ ***steps a), b), and c) are carried out at a temperature of 45±5°C; and wherein the antibody is rhuMAb E25.***" (emphasis added by the board; strike through and bold text representing deletion and addition respectively compared to point 1 on page 48 of the description of the divisional application as filed).

The feature "*recombinant humanized anti-IgE antibody*" is based on the passage on page 17, lines 22-23 of the description of the divisional application as filed.

The features relating to the concentrations of antibody are based on page 10, lines 14-27 of the description of the divisional application as filed.

The temperature of 45±5 °C is based on point 4 on page 48 of the description of the divisional application as filed.

Antibody rhuMAb E25 is based on examples 5 and 6 of the description of the divisional application as filed. Examples 5 and 6 are a pointer to combine the above features according to claim 1 of the main request.

Claims 2-10, 14-17 and 19 of the main request are based on points 3, 15-17, 6, 8, 11, 13, 22, 32, 33, 25-27, and 34-35 on pages 48-51 of the description of the divisional application as filed.

Claim 11-13, 18 and 20 of the main request are based on the following passages in the description of the divisional application as filed: page 16, lines 31-34; page 16, lines 26-27; page 16, lines 1-5; page 17, lines 8-9 and page 19, lines 31-33.

5. Article 76(1) EPC

Since the description of the divisional application as filed corresponds to the description and claims of the parent application as filed, the requirements of Article 76(1) EPC are also met.

6. Article 84 EPC and Rule 49(10) EPC

In its communication under Article 15(1) RPBA 2020, the board raised objections under Article 84 EPC and Rule 49(10) EPC. The board is satisfied that these objections have been met by the amendments carried out in the main request. The main request thus fulfils the requirements of Article 84 EPC and Rule 49(10) EPC.

7. Article 56

7.1 The subject-matter of claim 1 of the main request relates to a process for preparing concentrated formulations of rhuMAb E25. The process comprises a first step of ultrafiltering (UF1) of a preparation of rhuMAb E25, a second step of diafiltering (DF) and a third step of ultrafiltering (UF2).

7.2 D5 discloses a process for purifying an immunoglobulin fraction from a crude plasma protein fraction (D5, abstract). The process comprises a step of concentrating immunoglobulins by ultrafiltration (column 1, lines 54-56). The process comprises a first step of ultrafiltration (UF1, column 4, line 67 to column 5, line 7) followed by a molecular washing step

using the same ultrafiltration system in the presence of a buffer (column 5, lines 12-17). This molecular washing step is considered diafiltration (DF) as required by step b) of claim 1 of auxiliary request. The composition is further concentrated by a second ultrafiltration (UF2, column 5, lines 50-53). In the absence of any temperature disclosed in D5, each of UF1, DF and UF2 in that document would be assumed by the skilled person to be carried out at room temperature. In line with the examining division's decision, D5 represents the closest prior art.

7.3 Distinguishing features

The subject-matter of claim 1 of the main request differs from the process of D5 at least in that each of UF1, DF and UF2 is carried out at a temperature of 45±5 °C.

7.4 Technical effect and objective technical problem

The following conditions were used in the examples of the application as filed:

Example	UF1	DF	UF2
1	**20-25 °C**	40 °C	40 °C
comparative 2	**20-25 °C**	**RT**	**RT**
5	40-50 °C	40-50 °C	45°C±5 °C
6	40-50 °C	40-50 °C	45°C±5 °C

In examples 5 and 6 (according to claim 1 of the main request), each of UF1, DF and UF2 is carried out at a temperature of 40-50 °C as required by claim 1. In

example 1, only DF and UF2 are carried at 40 °C as required by claim 1, while UF1 is carried out at 20-25 °C, i.e. outside the temperature range defined in claim 1. In comparative example 2, each of UF1, DF and UF2 are carried out at room temperature (RT or 20-25 °C). This corresponds to the teaching of D5. The following results are shown for these examples:

Example	Concentration (g/L)	Yield (%)
1	120	86.1
comparative 2	104.4	73.1
5	170	99.2
6	167.08	97.4

Increased concentrations of rhuMAb E25 solution and increased yield are achieved for examples 5 and 6 (according to claim 1 of the main request) in comparison to example 1 (not according to claim 1 of the main request) and comparative example 2 (representing the general teaching of D5).

As submitted by the appellants, the objective technical problem may therefore be seen in the provision of a process for preparing a higher concentration of rhuMAb E25 with a higher yield.

In its decision (point 18.3.3), the examining division did not recognise the effect achieved by claim 1 of the main request. This is due to the fact that the distinguishing features were different (top of page 10 of the decision).

7.5 Non-obviousness

As set out above, D5 does not disclose any temperature for performing the filtration steps it describes and

does not teach how to improve the concentration and the yield of rhuMAb E25.

Even if D6 (paragraph 10 on page 33) teaches to increase temperature in a UF/DF process for heat stable proteins for reducing viscosity and increasing filtrate flux, meaning that the duration of the concentration process could be decreased, there is no teaching in D6 that an increased temperature would improve the yield and achieve a higher concentration of rhuMAb E25.

8. The board concludes that the subject-matter of claim 1, and by the same token all the remaining claims of the main request, involves an inventive step in view of D5 as the closest prior art.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with claims 1 to 20 of the main request filed as the second auxiliary request by letter dated 27 April 2022 and a description to be adapted.

The Registrar: The Chairman:

M. Schalow M. O. Müller

Decision electronically authenticated