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**Datasheet for the decision
of 15 May 2025**

Case Number: T 1474/23 - 3.3.08

Application Number: 14799930.4

Publication Number: 3063543

IPC: G01N33/68

Language of the proceedings: EN

Title of invention:

Competitive ligand binding assay for detecting neutralizing antibodies

Patent Proprietor:

Regeneron Pharmaceuticals, Inc.

Opponent:

Maiwald GmbH

Headword:

ligand binding assay/REGENERON PHARMACEUTICALS

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step (yes)

Decisions cited:

T 0840/17, T 2073/18, T 2733/19

Catchword:

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Beschwerdekammern

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

Case Number: T 1474/23 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 15 May 2025

Appellant: Maiwald GmbH
(Opponent) Elisenhof, Elisenstrasse 3
80335 München (DE)

Representative: Maiwald GmbH
Elisenhof
Elisenstraße 3
80335 München (DE)

Respondent: Regeneron Pharmaceuticals, Inc.
(Patent Proprietor) 777 Old Saw Mill River Road
Tarrytown, NY 10591 (US)

Representative: Reddie & Grose LLP
The White Chapel Building
10 Whitechapel High Street
London E1 8QS (GB)

Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
5 June 2023 concerning maintenance of the
European Patent No. 3063543 in amended form**

Composition of the Board:

Chair T. Sommerfeld
Members: B. Claes
D. Rogers

Summary of Facts and Submissions

- I. The appeal lodged by the opponent (appellant) lies from the interlocutory decision of the opposition division that European patent No. 3 063 543 entitled "*Competitive ligand binding assay for detecting neutralizing antibodies*", granted on European patent application No. 14799930.4, with the set of claims of the main request filed during the oral proceedings and the invention to which it related met the requirements of the EPC.
- II. At the end of the oral proceedings before the opposition division, five auxiliary requests were still pending, all filed by the patent proprietor prior to the oral proceedings (Minutes of oral proceedings, point 10 in combination with sections 2 and 5). Claims 1 and 2 of auxiliary request 5 are identical to claims 9 and 10 of the patent as granted.
- III. With the grounds of appeal, the appellant objected *inter alia* to the subject-matter of each claim of the main request for lack of inventive step (Article 56 EPC). Concerning claims 9 and 10 of the main request, the appellant made the following statement in the context of inventive step (see grounds of appeal, paragraph 186):

"Claims 9 and 10 lack inventive step for the reasons provided above in connection with claims 1, 3, and 8."

Concerning pending auxiliary request 5 (see section II.), the appellant made the following statement (page 43 of the grounds of appeal):

"V. AR5 filed 21 October 2022

AR5 has only claims 1 and 2, which correspond to claims 9 and 10 as granted.

As correctly concluded by the OD in the oral proceedings held on 10 November 2022, claim 10 as granted contravenes Article 123(2) EPC. Already for this reason, AR5 does not meet the requirements of the EPC."

- IV. In the reply to the appellant's grounds of appeal, the patent proprietor (respondent) provided arguments why the subject-matter of the claims of the main request *inter alia* involved an inventive step (Article 56 EPC) and submitted five new auxiliary requests each being an amended version of the corresponding auxiliary requests pending in the opposition proceedings.
- V. The parties were summoned to oral proceedings and subsequently the board issued a communication under Article 15(1) RPBA. Concerning auxiliary request 5 the board stated:

"28. The appellant's arguments concerning added subject-matter that may concern claim 2 of auxiliary request 5 concern claim 10 of the main request. Due to the absence of feature (d) in claim 2 of auxiliary request 5, these submissions are irrelevant.

29. Currently, the appellant has neither made an added subject-matter attack on claim 1 of auxiliary request 5 nor submitted particular and dedicated arguments why new auxiliary request 5 would not be allowable for other reasons.

30. *On appeal, the respondent has in particular made no arguments that the claimed subject-matter of auxiliary request 5 involves an inventive step. However, concerning the conclusions of the opposition division that claims 9 and 10 of the main request (are novel and) involve an inventive step (see section 5.5 of the appealed decision), the appellant has submitted on appeal that the subject-matter of these claims lack an inventive step for the reasons as submitted for claims 1, 3 and 8 of the main request (see grounds of appeal, paragraph 186).*

31. [...]

32. *As compared to claim 1 of the main request, claim 1 of auxiliary request 5 is limited to a method concerning the neutralising antibodies to the particular therapeutic monoclonal antibody sarilumab and a detection reagent which comprises labelled soluble IL-6 receptor α , both limitations which are mirrored in claim 3 of the main request which has been addressed by the appellant under inventive step in paragraphs 177 to 179 of the grounds of appeal by a further reference to the disclosure in documents D9 and D10."*

VI. In a letter dated 28 March 2025, filed in reply to the board's communication, the appellant stated in the final paragraph 52:

"Regarding AR-5 and the discussion of inventive step, the Board has acknowledged in point 30 that we are of the opinion (see point 186 of our GoA) that AR-5 does not involve an inventive step due to the same reasons as discussed for the Main Request. Further, in point 32

the Board has acknowledged that we are of the opinion that the amendments in AR-5 do not render AR-5 inventive as discussed in points 177 to 179 of our GoA."

- VII. Also in reply to the board's communication, by letter dated 12 April 2025, the respondent made further submissions and filed new auxiliary requests 1 to 34, auxiliary request 34 being identical to auxiliary request 5 filed with the grounds of appeal.
- VIII. At the end of the oral proceedings the respondent withdrew the main request and auxiliary requests 1 to 33 and requested that the decision under appeal be set aside and that the patent be maintained upon the basis of auxiliary request 34.
- IX. The appellant requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Auxiliary request 34

1. Auxiliary request 34 consists of two claims which are identical, respectively, to claims 1 and 2 of auxiliary request 5 filed with the reply to the grounds of appeal and to claims 9 and 10 of the former main request dealt with in the decision under appeal (see section II).
2. Since the appellant had no objections under Article 54 and 123(2) EPC to these claims on appeal, the sole contentious issue is whether or not the claimed subject-matter involves an inventive step (Article 56 EPC).

Inventive step

3. Claims 1, 3 and 8 to 10 of the former main request read:

"1. A method for detecting the presence of neutralizing antibodies to a **biotherapeutic protein** wherein the biotherapeutic protein has been administered to a patient in need thereof, comprising the steps of:
(a) combining a patient sample with a capture reagent comprising a **labeled biotherapeutic protein**, wherein the label facilitates binding to a surface; and,
(b) adding a detecting reagent, comprising a **labeled target of the biotherapeutic protein**, wherein a decreased signal relative to a negative control sample indicates the presence of a neutralizing antibody to the biotherapeutic protein, and wherein the patient sample is subjected to treatment with low pH prior to step (b) and wherein the treatment with low pH is followed by neutralization." (emphasis added by the board)

"3. The method of claim 1, wherein **the biotherapeutic protein is:**

- (a) a monoclonal antibody;
- (b) an anti-interleukin-6 receptor α (IL-6R α) monoclonal antibody and the target of the biotherapeutic protein is **an interleukin-6Ra** [sic] **(IL-6R α)** ;
- (c) sarilumab or tocilizumab; or
- (d) **sarilumab.**" (emphasis added by the board)

"8. The method of any one of the preceding claims, wherein the assay comprises a precision ranging from 1-8% with the following characteristics:

sensitivity = ~150 ng/mL, drug tolerance = ~500 ng/mL, and target interference = ~1 µg/mL.

9. A method for detecting the presence of neutralizing antibodies to **sarilumab**, wherein sarilumab has been administered to a patient in need thereof, comprising the steps of:

- (a) combining a patient serum sample with a capture reagent comprising **biotinylated sarilumab** wherein the biotin label facilitates binding to a surface;
- (b) subjecting the combined patient serum sample and capture reagent to treatment with low pH, followed by a neutralizing step; and
- (c) adding a detecting reagent, wherein the detecting reagent comprises **labeled soluble IL-6 receptor α** , wherein a decreased signal relative to a negative control sample indicates the presence of a neutralizing antibody to sarilumab.

10. The method of claim 9, wherein:

- (a) the detection reagent is ruthenium labeled soluble IL-6 receptor α ; and/or
- (b) the patient is suffering from rheumatoid arthritis; and/or
- (c) the assay exhibits a sensitivity tolerance of about 150 ng/mL, a drug tolerance of about 500 ng/mL, and a target interference tolerance of about 1 µg/mL." (emphasis added by the board)

4. Compared to independent claim 1 of the main request, it is now specified in the method of claim 1 for detecting the presence of neutralising antibodies to a biotherapeutic protein of independent claim 1 (see claim 9 of the main request above) that the biotherapeutic protein is "sarilumab", that the labeled biotherapeutic protein in the detecting reagent is

"biotinylated sarilumab" and the labeled target of the biotherapeutic protein is "labeled soluble IL-6 receptor α ".

5. As can be taken from section III. above, the appellant limited its submissions on appeal to stating that the subject-matter of claims 9 and 10 of the main request lacked inventive step for the same reasons as claims 1, 3 and 8 of the main request.

6. Concerning claim 3 of the main request the appellant submitted in paragraphs 177 to 179 of its grounds of appeal:

*"Additionally, the skilled person is aware that the cytokine **IL-6 signals via membrane-bound and soluble IL-6R**, see, e.g., D7 (Abstract on page 15 and Summary on page 20); basis patent on sarilumab, EP 2 041 177 B1 (D8, paragraph [0001]).*

*Both anti-IL-6R monoclonal antibodies, **sarilumab** and tocilizumab, **bind to** both soluble and membrane-bound **IL-6R**, see, e.g., D9 (page 20, left column, third paragraph); D10 (Table 1). Sarilumab and tocilizumab are also known to have essentially no complement dependent cytotoxicity activity or antibody-dependent cellular cytotoxicity activity.*

***Hence**, the skilled person knew at the relevant date that a non-cell based approach was appropriate.*

***Choosing sarilumab** or tocilizumab as the monoclonal antibody **cannot render any of claims 3 to 5 inventive over D2.**" (emphasis added by the board)*

7. However, the submission of the appellant fails to address the very features of the amendments in claim 1

of auxiliary request 34 that differ from claim 1 of the main request. Indeed, although the statement may be acknowledged to refer to "sarilumab" as the biotherapeutic protein for the claimed method, it is silent on the amendments that the labeled biotherapeutic protein in the detecting reagent is "**biotinylated**" sarilumab, the labeled target of the biotherapeutic protein is labeled "**soluble**" IL-6 receptor and is the "**α**" IL-6 receptor.

8. Claim 8 of the former main request dealt with in the decision under appeal, to which the appellant has also referred in the context of inventive step (see section III.), relates to dependent claim 2 and is irrelevant for the assessment of inventive step of claim 1 of auxiliary request 34.
9. Neither during the remainder of the written proceedings (see section VI. above), nor at the oral proceedings, has the appellant made further substantive submissions in the context of inventive step of the subject-matter of claims 1 and 2.
10. The board has accordingly not seen convincing arguments from the side of the appellant that the subject-matter of claim 1, including these amendments, lacks an inventive step. As claim 2 is dependent on claim 1, the same is valid for this claim.
11. It is established in the case law of the Boards of Appeal, and this board agrees, that, if an objection of lack of inventive step does not address all distinguishing features of a claim, the objection may be considered insufficient or unpersuasive and may then, for this reason, be dismissed by the board (see

e.g. decisions T0840/17, Reasons 6.4; T2073/18, Reasons 3 and T2733/19, Reasons 5).

12. The board hence sees no reason to deviate from the decision of the opposition division that the subject-matter of these claims (identical to claims 9 and 10 of the former main request) involves an inventive step.
13. Auxiliary request 34 is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted:
Claims:
No. 1 and 2 of auxiliary request 34 filed under cover of a letter dated 12 April 2025.

The Registrar:

The Chair:



C. Rodríguez Rodríguez

T. Sommerfeld

Decision electronically authenticated