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Datasheet for the decision of 18 June 2019

Case Number: T 1398/14 - 3.3.01

Application Number: 05824356.9

Publication Number: 1853921

IPC: G01N33/68

Language of the proceedings: EN

Title of invention:
DETECTION OF A THERAPEUTIC ANTIBODY IN AN EXPERIMENTAL ANIMAL

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponents:
MorphoSys AG
Novartis AG

Headword:
Detection of therapeutic antibody/HOFFMANN-LA ROCHE

Relevant legal provisions:
RPBA Art. 13(1)
EPC Art. 56

Keyword:
Late-filed request - admitted (yes)
Inventive step - (yes)

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Case Number: T 1398/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 18 June 2019

Appellant: (Patent Proprietor)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent: (Opponent 1)	MorphoSys AG Lena-Christ-Str. 48 82152 Planegg/Martinsried (DE)
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Respondent: (Opponent 2)	Novartis AG Lichtstrasse 35 4065 Basel (CH)
Representative:	Marshall, Cameron John Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 April 2014 concerning maintenance of the European Patent No. 1853921 in amended form**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	T. Sommerfeld
	P. de Heij

Summary of Facts and Submissions

I. European patent 1853921 is based on application 05824356.9, which was filed as an international application and published as WO 2006/066912. The patent is entitled "Detection of a therapeutic antibody in an experimental animal" and was granted with 10 claims.

II. Two oppositions were filed against the granted patent, both opponents requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54(2) and 56 EPC and Article 100(a) EPC), and lack of sufficiency of disclosure (Article 100(b) EPC).

III. By an interlocutory decision announced at oral proceedings, the opposition division decided that the patent could be maintained in amended form on the basis of auxiliary request 1, filed as auxiliary request 12 by letter of 10 October 2013 (Articles 101(3)(a) and 106(2) EPC).

The opposition division considered that the claims according to the main request (filed as auxiliary request 8 with the letter of 10 October 2013) lacked inventive step but fulfilled the requirements of Articles 54 and 83 EPC.

IV. The patent proprietor (appellant) lodged an appeal against that decision. With the statement of the grounds of appeal, the appellant requested that the patent be maintained on the basis of the main request or, alternatively, according to the auxiliary request (which was identical to the auxiliary request upheld by the opposition division), both filed with the grounds of appeal.

V. Both opponents 1 and 2 (respondents) replied to the patentee's statement of grounds of appeal, opponent 2 requesting that the appeal be dismissed and opponent 1 requesting that the patent be revoked in its entirety. With a further letter, dated 23 March 2015, opponent 1 submitted further experimental data.

VI. Summons for oral proceedings before the board were issued with an accompanying communication summarising some of the issues to be discussed.

VII. Respondent-opponent 1 replied by letter dated 14 May 2019.

VIII. The appellant replied by letter dated 17 May 2019, requesting that the late-filed experimental data submitted by respondent-opponent 1 not be admitted. It also filed new experimental data (second declaration of Dr Stubenrauch) and a new auxiliary request 1, requesting that they be admitted into the proceedings as a reaction to the late-filed submissions of respondent-opponent 1. It moreover re-submitted the main request and the previous auxiliary request as auxiliary request 2.

IX. Oral proceedings before the board took place as scheduled. During the oral proceedings, the appellant again requested that auxiliary request 1 and the second declaration of Dr Stubenrauch be admitted into the proceedings and that the late-filed experimental data of respondent-opponent 1, filed with the letter dated 23 March 2015, not be admitted into the proceedings in the event that the board decided not to admit the second declaration of Dr Stubenrauch. It later replaced its main request by auxiliary request 1 filed on

17 May 2019. Respondent-opponent 1 requested that its submissions filed with the letter of 23 March 2015 be admitted into the proceedings, that auxiliary request 1 (the later main request) be admitted only if said submissions were also admitted and that the second part of Dr Stubenrauch's declaration not be admitted. Respondent-opponent 2 requested that neither auxiliary request 1 (the later main request) nor the declaration of Dr Stubenrauch be admitted into the proceedings. At the end of oral proceedings the chairwoman announced the board's decision.

X. Claim 1 of the **main request** (filed as auxiliary request 1 with the letter of 17 May 2019) reads as follows:

"1. A method of detecting a human or humanized therapeutic monoclonal antibody which is intended for use in a human being in a sample obtained from an experimental animal comprising the steps of
a) providing the sample to be analyzed,
b) incubating said sample with an antibody binding to said therapeutic antibody and not binding to the immunoglobulin of said experimental animal,
c) optionally incubating said sample with a reagent appropriate for the selective detection of total, active or antigen-bound therapeutic antibody, and
d) correlating the complex formed in (b) or (c) to the concentration of said therapeutic antibody,
wherein said experimental animal is selected from the group comprising the members of the families of marmosets and tamarins, old world monkeys, dwarf and mouse lemurs, gibbons and lesser apes, true lemurs, as well as crossings thereof, and wherein said antibody binding to the therapeutic antibody and not binding to the immunoglobulin of the experimental animal is the antibody deposited in DSM ACC 2708."

XI. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

D3 Stephens et al. 1995, Immunology 85, 668-674
D4 Black et al. 1993, Immunol. Lett. 37, 207-213
D6 Stubenrauch et al. 2009, J. Pharmaceut. Biomed. Anal. 49, 1003-1008
D8 Excerpt from Serotec catalogue from 1995
D12 Product description for HP6023 (SouthernBiotech)
D13 Product description for HP6025 (Southern Biotech)
D16 Research Diagnostics' product page for R10Z8E9 from 1997 (internet archive)
D22 Hazlewood et al. 1993, Clin. Exp. Immunol. 93, 157-164

XII. The appellant's submissions, in so far as they are relevant to the present decision, may be summarised as follows:

The new auxiliary request 1 (and later main request) should be admitted into the proceedings as it was simply a very narrow version of the main request and had been filed as a reaction to the late-filed submissions of respondent-opponent 1. Even though novelty and sufficiency of disclosure had not been discussed, the amendments introduced in this request still addressed inventive step issues that had been raised for the first time during appeal. Moreover, this request had been already presented before the first instance.

Regarding inventive step, the technical problem should be formulated as the provision of an improved method over that of D3, since the use of the claimed antibody

conferred advantages on the method of D3. First, the fact that R10Z8E9 (the antibody deposited in DSM ACC 2708) was pan-IgG-specific was advantageous because it enabled its use for all classes of IgG (paragraph [0044] of the patent in suit). Second, the epitope was highly selective, as shown in Tables 2c and 2d of the patent, while D3 did not provide any information concerning selectivity. Third, the LLOQ of the claimed method was much better than that of D3's method: Tables 4, 6 and 8 and Figures 3, 5, and 9 of the patent in suit showed that there was a linear correlation even at very low concentrations. The claimed solution would not be obvious because, although the R10Z8E9 antibody was known in the prior art as an anti-human immunoglobulin antibody as early as in 1993 (D22, page 158, right-hand column, second paragraph) and commercially available (D16), nothing else was known about its selectivity, let alone that it had such a high selectivity for human immunoglobulin. Moreover, it would have been expected to have lower selectivity than the antibody used in the method of D3, based on the fact that it was a pan-IgG-specific antibody rather than an isotype-specific antibody. Therefore, the skilled person, starting from D3, would have rather chosen any of the many other antibodies taught in D4 to have the desired selectivity. The fact that R10Z8E9 was not listed in D4 and that it had never been used in the prior art in a method as disclosed in D3 was further evidence that the skilled person would not have considered it suitable for use in detection and quantification methods. The suitability for ELISA mentioned in D16 would not be an indication of high selectivity.

XIII. The respondents' arguments, in so far as they are relevant to the present decision, may be summarised as follows:

Respondent-opponent 2 objected to the admission of auxiliary request 1 (and later main request) filed with the letter of 17 May 2019, arguing that its late filing was detrimental for the party's legal certainty. There was no justification for its admission because it had been filed conditionally only in the event that the new submissions of respondent-opponent 1 were taken into consideration; since neither these submissions nor the related novelty objection had been discussed at all there was no reason to admit the request.

As for inventive step, both opponents formulated the technical problem as being the provision of an alternative to the method disclosed in D3. None of the alleged advantages of R10Z8E9 over D3's antibodies was reflected in the claim nor had they been demonstrated in the patent (e.g. absence of the washing step). As for the LLOQ, the values given in the patent could not be compared with those of D3 because the conditions, and in particular the plasma sample dilutions, were different or not known: Table 6 and paragraph [0070] (Example 3); pages 669 and 670 of D3. The alleged decrease of the noise-to-signal ratio in the patent was not necessarily due to a higher selectivity of the antibody but rather appeared to be linked to the detection system, since the cross-reactivity was inter-specific (paragraph [0070]). From D6, it was apparent that the LLOQ as calculated in the patent was not realistic (D6, page 1007, right-hand column, last two lines) and in any case it was only valid for the sandwich-type assay depicted in Figure 1. The R10Z8E9 antibody, which was commercially available and known to be selective for human IgG, even being offered for ELISA (D16), would be an obvious alternative to the HP6023 antibody in the method of D3. The fact that it

was not listed in D4 could have different reasons; most likely it was just not made available to the authors at that time. The pan-specificity of R10Z8E9 would not have been seen as a disadvantage in the context of measuring the specific therapeutic antibody of D3. Commercially available antibodies were those that had low cross-reactivities (D12, D13), since companies sold antibodies known to work well in assays.

XIV. The appellant (patentee) requested at the end of the oral proceedings that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, filed with the letter of 17 May 2019 as auxiliary request 1.

The respondents (opponents) requested that the appeal be dismissed. In addition, respondent-opponent 2 requested that auxiliary request 1, filed with the letter of 17 May 2019, and the second declaration of Dr. Stubenrauch not be admitted into the proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. Admissibility of late-filed submissions

2.1 Admission of the late-filed submissions of respondent-opponent 1 (filed with the letter of 23 March 2015) was not discussed at oral proceedings, as these submissions only concerned novelty of the then main request and were not relevant for inventive step, which was the only issue dealt with in respect of the present main request.

2.2 As for the second declaration of Dr Stubenrauch, this was filed by the appellant with the letter dated 17 May 2019 as a reaction to the above-mentioned submissions of respondent-opponent 1, but at oral proceedings the appellant also intended to rely on it in the discussion of inventive step of the then main request. After hearing the arguments from the parties, the board decided at oral proceedings not to admit this declaration into the proceedings. However, in view of the fact that said declaration plays no role for the present decision, which concerns only the claim request which was filed as auxiliary request 1 with the letter dated 17 May 2019, no reasoning is given here for the board's discretionary decision not to admit it.

2.3 The board furthermore decided to admit the appellant's new line of argument concerning antibody HP6064's binding to the same epitope as antibody R10Z8E9. As this argument was also only relevant for the then main request, which was later withdrawn, again no reasoning for this decision is required.

3. Admission of the main request (filed as auxiliary request 1 with letter of 17 May 2019)

3.1 Article 13(1) RPBA stipulates that any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the board's discretion. The discretion shall be exercised in view of inter alia the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy.

3.2 Although the present claim request was filed just one month before the date scheduled for oral proceedings,

the board notes that it is a simplification of the previous main request, restricting the broad definition of the antibody to be used in the detection method of claim 1 to a single specific antibody. While in the previous main request the antibody to be used was defined as "a monoclonal antibody binding to the same epitope as the antibody deposited in DSM ACC 2708", in the present request it is defined as "the antibody deposited in DSM ACC 2708". This amendment clearly addresses the respondents' objections to the previous main request regarding novelty and sufficiency of disclosure and does not raise new issues.

3.3 The board agrees with respondent-opponent 2 that this request could have been filed earlier since the new objections it addresses have been on file since 2015. However, its filing as a precaution just one month before oral proceedings was not detrimental to the respondent's legal certainty because in fact an even broader request (namely the previous main request) has been on file since the beginning of the appeal proceedings. Its late-filing could not be considered to impose an undue burden on the respondents either since the claimed subject-matter was a limited version of that covered by the previous main request, restricted to a specific antibody which had been the focus of the discussion during opposition and appeal proceedings. Moreover, even though the request had originally been filed as a reaction to new novelty objections, which in the end have not been discussed at all, its admission was still justified in view of the fact that the respondents had also put forward new arguments, in the context of inventive step, regarding the epitope definition and what antibodies were covered by the main request. Hence, this amendment also served to address said new line of argumentation under inventive step.

3.4 For these reasons, the board decided to admit the present main request (filed as auxiliary request 1 with the letter of 17 May 2019) into the proceedings (Article 13(1) RPBA).

4. Inventive step

4.1 The present patent is directed to a method of detecting a human or humanised therapeutic antibody in a sample obtained from an experimental animal, by using a monoclonal antibody binding to said therapeutic antibody and not binding to the immunoglobulin of said experimental animal (patent, paragraph [0001]), said antibody being, according to present claim 1, the antibody deposited in DSM ACC 2708. In the more advanced stages of drug development, especially before introduction of the drug as medication for human beings, higher mammals, including monkeys and other apes, may have to be included in pre-clinical studies (paragraph [0005]). In the case of human therapeutic antibodies tested in such experimental animals, the structural similarity between human immunoglobulins and ape immunoglobulins increases the risk of cross-reactivity and therefore of a higher background noise when performing pharmacokinetic studies on the tested therapeutic antibodies, since said studies are usually carried out using anti-human immunoglobulin detection antibodies. Therefore, it would be advantageous to use detection antibodies which are highly selective for human immunoglobulins and do not cross-react with the immunoglobulins of the experimental animal. The detection antibody as defined in the claim, which is the antibody deposited as DSM ACC 2708, is one such antibody, having been found by the inventors to bind to an epitope that is present on all classes of human

immunoglobulin of class G but not present on the immunoglobulin of any of the relevant experimental animals except on the IgG of chimpanzees (paragraph [0044]).

4.2 Document D3 is the closest prior art. It is concerned with the study of the pharmacokinetics of one particular humanised therapeutic antibody, and discloses on page 670 a pharmacokinetic ELISA which comprises all the features of the claimed method, with the only difference being that a different monoclonal antibody is used for detection of the human or humanised monoclonal therapeutic antibody, i.e. it does not use an antibody deposited as DSM ACC 2708 (agreed by all parties). D3 uses a "murine monoclonal antibody to human IgG4 (Serotec, Kiddlington, UK)", which is not further identified. D8, which is the 1995 catalogue of Serotec, Kiddlington, UK, renders it apparent that the antibody used in D3 is the so-called mAb "HP6023". According to D4 (Table 1 on page 210), HP6023 specifically binds to human IgG4 without cross-reacting with immunoglobulin from lesser apes or old world monkeys.

4.3 There are no data in the patent or elsewhere on file directly comparing the use of an antibody as claimed and the antibody HP6023 of D3 in a method as claimed. The alleged advantages of the claimed antibody are linked to its high selectivity for human immunoglobulin over immunoglobulin from lesser ape species; however, such advantages would also be expected for HP6023, which displays the same selectivity. Hence, there is no technical effect associated with the distinguishing feature. The technical problem is thus to be formulated as the provision of an alternative method for detection of a human or humanised monoclonal therapeutic antibody

in the sample of experimental animals, which belong to the group of lesser apes and old world monkeys. The solution is a method as claimed, using the antibody deposited as DSM ACC 2708, and in view of the data presented in the patent (examples) the board is satisfied that the problem has been plausibly solved.

4.4 The deposited antibody DSM ACC 2708 was known in the prior art as R10Z8E9, a mouse monoclonal antibody to human IgG that had been disclosed in 1993 (D22) and was commercially available as early as in 1997, as evidenced by D16. Thus, the skilled person would have *a priori* considered such an antibody as potentially useful for detecting and quantifying human immunoglobulin. However, there was no information at all in the prior art about the selectivity of the R10Z8E9 antibody, in particular that it was highly selective for human immunoglobulin and had low cross-reactivity for immunoglobulins from lesser ape species. The board disagrees with the respondents' arguments that the fact that the antibody had been commercially offered for ELISA (D16) was indicative of such selectivity. It is true that commercial antibodies are expected to fulfil a number of requirements, but a high selectivity is not necessarily one of them, unless otherwise stated. In this context, it is noted that antibodies HP6023 and HP6025 (both commercially available: D12 and D13, respectively), shown in D4 to have a high selectivity (table on page 610), are just two examples among many commercially available antibodies. This is apparent e.g. from Table 1 of the patent, which lists a number of different commercially available antibodies, all of which have a much lower selectivity than the antibody of the invention.

4.5 Hence, when seeking to find a solution to the technical problem as posed above, namely the provision of an alternative method for the detection of a human or humanised monoclonal therapeutic antibody in the sample of experimental animals, which belong to the group of lesser apes and old world monkeys, the skilled person would not be prompted to select the R10Z8E9 antibody because they would have no reason to expect that this antibody would have the same advantages of high selectivity for human immunoglobulin as the antibody used in D3. Therefore, the skilled person would not have considered this antibody to be a suitable alternative to the antibody of D3; instead, they would have considered using any of the many antibodies listed in D4 and shown in Table 1 of D4 to have said desired selectivity. Accordingly, the selection of the specific antibody as claimed was not obvious.

4.6 The claims of the present request are thus considered to involve an inventive step.

4.7 There were no further objections to this request from the opponents, and the board has none either. Hence the present sole request is considered to comply with the requirements of the EPC.

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 set of claims of the main request, filed as auxiliary request 1 with the letter dated 17 May 2019, and a description to be adapted thereto.

The Registrar: The Chairwoman:

M. Schalow M. Pregetter

Decision electronically authenticated