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Datasheet for the decision of 7 February 2019

Case Number: T 0139/16 - 3.3.07

Application Number: 10737891.1

Publication Number: 2459167

IPC: A61K9/19, A61K39/395, A61K47/18, A61K47/26, C07K16/32, A61K47/42, A61K9/00

Language of the proceedings: EN

Title of invention:
SUBCUTANEOUS ANTI-HER2 ANTIBODY FORMULATION

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponent:
HGF Limited

Headword:
Anti-HER2 antibody formulations / HOFFMANN-LA ROCHE

Relevant legal provisions:
EPC Art. 113(1), 56, 54, 123(2), 100(b)
RPBA Art. 13(1), 13(3)

Keyword:

Inventive step - main request (yes)
Oral proceedings - held in absence of appellant
Admission of documents in first instance proceedings - proper exercise of discretion (yes)
Novelty - (yes)
Sufficiency of disclosure - (yes)
Amendments - added subject-matter (no)

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Case Number: T 0139/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 February 2019

Appellant: (Opponent)	HGF Limited Saviour House 9 St Saviour Gate York YO1 8NQ (GB)
Representative:	HGF Limited 1 City Walk Leeds LS11 9DX (GB)
Respondent: (Patent Proprietor)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 23 November 2015 concerning maintenance of the European Patent No. 2459167 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	Y. Podbielski

Summary of Facts and Submissions

I. The appeal of the opponent lies against the interlocutory decision of the opposition division finding that European patent No. 2 459 167 in amended form met the requirements of the EPC.

II. The patent in suit was granted on the basis of 23 claims. Independent claim 1 related to highly concentrated, stable pharmaceutical formulations for subcutaneous injection comprising, in particular, an anti-HER2 antibody and a hyaluronidase enzyme.

III. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, and that it was not sufficiently disclosed.

IV. The decision under appeal was based on the main request filed by letter dated 19 August 2015.

The following documents were cited *inter alia* in the decision under appeal:

D1: US 2006/104968
D2: US 2007/071675
D4: US 6267958
D8: US 2006/088523
D19: Pharm Res (2003) 20(9); 1325-1336
D21: Declaration of Prof. Dr. Frieß (including Annexes A and B and Exhibits 1-5)
D22: Declaration of Dr. Adler (including Annex A)
D23: Ratner, Nature Biotechnology 28(4), 298
D24: Priority document EP 09 167 025.7

According to the decision under appeal:

(a) documents D21-D23 were admitted into the proceedings;

(b) the main request met the requirements of sufficiency of disclosure and novelty over D2;

(c) the subject-matter of the main request differed from the anti-HER2 antibodies formulations of the closest prior art D8 by the hyaluronidase enzyme. Neither a combination with the teaching of D1, nor with the teaching of D2 or D23 led to the claimed invention in an obvious manner. This conclusion was not modified if the skilled person were to start from D4 or D2.

V. The opponent (appellant) lodged an appeal against this decision. In its statement of grounds of appeal, the appellant *inter alia* contested the opposition division's decision to admit documents D21 and D22 filed 8 weeks before oral proceedings and considered that its right to be heard was violated by their admission.

VI. In its reply to the statement of grounds of appeal, the patent proprietor (respondent) defended its case on the basis of a main request (maintenance of the patent in the version held allowable by the opposition division) and 27 auxiliary requests.

VII. By letter dated 28 November 2016, the appellant contested the admissibility of auxiliary requests 6-27.

VIII. The Board issued a communication pursuant to Article 15(1) RPBA on 11 December 2018. In it, the Board

expressed *inter alia* the preliminary opinion that the appellant's main request and auxiliary requests 1-5 did not meet the requirements of Article 56 EPC. It further added that a rejection of auxiliary requests 6-27 as inadmissible did not appear to be justified by the provisions of Article 12(4) RPBA. However, these auxiliary requests did not appear to meet the requirements of the EPC. Auxiliary request 15 in particular was considered to contravene Article 123(3) EPC.

IX. By letter dated 7 January 2019, the respondent filed a new main request and a new auxiliary request 1. Claim 1 of the main request read as follows:

"A liquid, highly concentrated, stable pharmaceutical anti-HER2 antibody formulation for subcutaneous injection comprising 120 mg/ml Trastuzumab, 20 mM L-histidine/HCl pH 5.5, 210 mM α,α-trehalose dihydrate, 10 mM methionine, 0.04% polysorbate 20 and 2'000 U/ml rHuPH20".

X. Oral proceedings were held on 7 February 2019. As announced by letter dated 14 December 2018, the appellant did not attend these proceedings.

XI. The appellant did not comment on the respondent's main request filed by letter dated 7 January 2019. The appellant's earlier arguments, insofar as relevant to the present decision, can be summarized as follows:

(a) Both D21 and D22 contained experimental data and were filed by the respondent on the last day set by the opposition division pursuant to Rule 116(1) EPC. The opposition division's decision to admit D21 and D22 into the proceedings violated the

appellant's right to be heard because it was not afforded sufficient time to conduct comparative experimental testing.

(b) The subject-matter of claim 1 of the patent as maintained by the opposition division lacked novelty over D2.

(c) The closest prior art D8 disclosed highly concentrated, stable pertuzumab pharmaceutical compositions. The difference between the subject-matter of the patent as maintained and the disclosure of D8 resided in the inclusion of a hyaluronidase enzyme. This was suggested by D1, which described the co-formulation, for sub-cutaneous administration, of a variety of parenterally administered therapeutic agents with a hyaluronidase enzyme. No conclusion could be drawn from D21 regarding aggregation when the anti-HER2 antibody and the hyaluronidase protein were formulated together. Hence the skilled person was not deterred from considering the combination of said two proteins. Alternatively, since the claimed subject-matter was not entitled to the priority date, D23 belonged to the state of the art and likewise suggested the co-formulation of an anti-HER2 antibody and a hyaluronidase enzyme.

(d) In light of the breadth of the claim and in particular the large pH range, obtaining a stable formulation suitable for subcutaneous injection over the whole claimed scope represented an undue burden for the skilled person.

XII. The respondent's arguments, insofar as relevant to the present decision, can be summarized as follows.

(a) The main request filed on 7 January 2019 derived from previous auxiliary request 15, whereby the term "for subcutaneous injection" was introduced in claim 1. Accordingly, the main request addressed the objection raised by the Board under Article 123(3) EPC against previous auxiliary request 15, and should be admitted into the proceedings.

(b) The main request also addressed the Board's concern with respect to inventive step of the previously pending broader claim requests. The closest prior art should be the exemplary pharmaceutical composition 10 of D8, from which the claimed subject-matter, exemplified by formulation X of the examples, differed *inter alia* by the presence of a hyaluronidase enzyme and of methionine. A comparison of formulations X, A and G in the examples of the patent in suit showed that the addition of a hyaluronidase enzyme in a Trastuzumab (an anti-HER2 antibody) formulation containing methionine did not lead to the formation of Trastuzumab aggregates or to loss of stability. D22 demonstrated that methionine played an active role in avoiding the formation of aggregates in the claimed formulation and stabilised the hyaluronidase enzyme activity. The objective technical problem was the provision of highly concentrated, stable anti-HER2 antibody pharmaceutical formulations that are ready for subcutaneous administration. The claimed co-formulation, resulting from an increase in antibody concentration and the addition of a hyaluronidaze enzyme in the claimed amount and of

methionine, was not rendered obvious by D8, D1 or D23. The skilled person would have been concerned that protein-protein interactions between the anti-HER2 antibody and the hyaluronidase enzyme would lead to detrimental aggregation, as shown in D21.

XIII. The appellant requested in writing that the decision under appeal be set aside and the patent be revoked. It also requested that auxiliary requests 6-27 (filed with the reply to the grounds of appeal dated 10 August 2016) not be admitted into the proceedings, and that documents D21 and D22 not be admitted into the appeal proceedings.

XIV. The respondent requested that the patent be maintained on the basis of the main request or auxiliary request 1, both filed with letter dated 7 January 2019, or on the basis of one of auxiliary requests 2-29 filed as a main request and auxiliary requests 1-27 with the reply to the grounds of appeal dated 10 August 2016.

Reasons for the Decision

1. Absence of the appellant at oral proceedings

As announced in its letter dated 14 December 2018, the appellant did not attend the oral proceedings.

In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the oral proceedings were held without the appellant. By its decision not to attend the oral proceedings, the appellant has chosen not to make any further submissions during such proceedings.

In the present case, the duly summoned appellant has to be treated as relying only on its written case.

2. Admission of D21 and D22

The appellant alleges that the opposition division wrongly exercised its discretion to admit documents D21 and D22 into the proceedings, and that by doing so it violated the appellant's right to be heard.

The respondent had filed documents D21 and D22 on 19 August 2015, two months before the date of the oral proceedings, which was also the last day set by the opposition division under Rule 116(1) EPC for making final submissions. Document D21, the Declaration of Prof. Dr Wolfgang Frieß, refers to exhibits 3-5 which include calculations of the isoelectric points of the relevant enzymes. D22, the declaration of Dr Michael Adler, describes experiments concerning the impact of methionine on the hyaluronidase enzyme activity/ stability. The formulations used in that experiment had been stored for 8 weeks. The appellant says that by admitting these documents its right to be heard was violated as it had not had an opportunity to respond with its own experimental data.

When exercising its discretion under Article 114(2) EPC, the opposition division considered primarily whether the documents were *prima facie* relevant. It also gave consideration to the question whether the appellant had a reasonable opportunity to respond. The opposition division thus took the right criteria into account when exercising its discretion. The question remains whether the opposition division exercised its discretion in an unreasonable way and violated the appellant's right to be heard.

The opposition division concluded that D21 and D22 were *prima facie* relevant. In the Board's view, the relevance of D21 is apparent from the fact that the opposition division relied on D21 in its line of reasoning on inventive step (point 9.4.4 of the reasons of the decision under appeal). The relevance of D22 to support an inventive step of the auxiliary requests had been acknowledged by the appellant itself during the oral proceedings (point 6 of the minutes).

It appears from the minutes of the oral proceedings that the emphasis of the discussion on the time required by the appellant to carry out its own experiments focused on the issue of the calculation of the isoelectric point of the concerned proteins (see point 6 of the minutes). The opposition division concluded that no long-lasting experiments would have been necessary in reaction to D21 as the experimental determination of isoelectric points could be done within a few hours and D21 had been submitted two months prior to the oral proceedings. The Board sees nothing unreasonable in this conclusion. In addition, the opposition division pointed out that the appellant had not submitted that it intended to carry out experimental tests (see point 2.1 of the reasons of the decision under appeal).

The Board notes in this regard that the appellant had at no time prior to the oral proceedings indicated that it wished to carry out experimental tests in response to D21 and D22. Indeed, it had made no observations on the filing of D21 and D22. Even in the letter dated 2 October 2015, in which the appellant addressed the criticism of the respondent concerning the late filing of document D23 by the appellant, no comment was made

on the submission of documents D21 and D22. There was no request for the adjournment of oral proceedings in view of the need to respond to D21 and D22 by producing its own experiments, nor was there any indication that any experiments had in fact commenced. Indeed, no experimental data was produced by the appellant in reply to D21 and D22, not even during appeal proceedings.

In view of the above, the Board finds that the opposition division did not exercise its discretion in an unreasonable way and that the appellant's right to be heard has not been violated. Accordingly, the appellant's request to set aside the opposition division's decision to admit documents D21 and D22 into the proceedings is rejected with the consequence that these documents form part of the appeal proceedings.

Main request

3. Admission

The main request was filed by letter dated 7 January 2019, i.e. after the respondent had filed its reply to the appellant’s grounds of appeal and after oral proceedings had been arranged. The provision of Articles 13(1) and 13(3) RPBA are therefore applicable to its admission.

The main request derives from auxiliary request 15. That request had been filed during the first instance proceedings as auxiliary request 9 on the last day set by the opposition division under Rule 116(1) EPC, and been re-filed with the reply to the grounds of appeal. It thus forms part of the appeal proceedings (Article 12(4) RPBA). In its communication the Board had raised

a new objection to auxiliary request 15, which was based on Article 123(3) EPC (see point 10.3 of the communication). The main request constitutes the respondent's answer to this objection. The respondent added the words "for subcutaneous injection" to claim 1 and deleted dependent claim 2. These amendments to previous auxiliary request 15 are of low complexity, they appear to solve the problem raised by the Board and do not give rise to new objections. The main request is thus admitted into the proceedings.

4. Article 123(2) and (3) EPC

Claim 1 of the main request results from the limitation of claim 1 of patent in suit to the particular formulation X shown on page 65 of the description as filed, with additionally the introduction of the feature "liquid form" disclosed in claim 17 of the application as filed. Compliance with the requirements of Article 123(2) EPC was not contested by the appellant and is not questioned by the Board.

The feature "for subcutaneous injection", which was present in the claims as granted and in the claims as maintained by the department of first instance, has been reintroduced into claim 1 of the main request. Accordingly the main request contravenes neither Article 123(3) EPC nor the principle of prohibition of reformatio in pejus.

5. Article 100(a) EPC, novelty

The appellant had raised an objection of lack of novelty over document D2 in respect of the respondent's earlier, broader requests. D2 does not anticipate the subject-matter of the present main request for the

following reasons: to arrive at the subject-matter of claim 1, several selections from D2 are necessary, namely the selection of the antibody trastuzumab from the list of paragraph [0112] together with further selections from paragraph [0184] regarding the presence of the further components. Furthermore, the particular amounts defined in claim 1 for each component are not shown in D2, let alone in combination. The requirement of novelty is thus met.

6. Article 100(a) EPC, inventive step

6.1 The problem underlying the claimed invention is the provision of highly concentrated, stable pharmaceutical formulations of active anti-HER2 antibody for subcutaneous injection.

6.2 In agreement with both parties, the Board considers document D8 as the closest prior art.

Within D8, the embodiment coming closest to the claimed invention is not the low concentration formulation of example 10, but rather examples 3 and 7 describing stable high concentration anti-HER2 antibody (Pertuzumab) liquid formulations comprising

(i) 100mg/ml of the anti-HER2 antibody Pertuzumab,
(ii) 10mM of an histidine.HCl buffer agent providing a pH of 6.0,
(iii) 240mM sucrose as stabilizer, and
(iv) 0.02% nonionic surfactant (polysorbate 20).

The Board notes that the concentration of the above prior art formulations (100mg/ml antibody) makes them substantially as suitable for subcutaneous injection as the claimed formulation (120mg/ml); their suitability

for subcutaneous or intramuscular administration is in any case explicitly mentioned in D8 (cf. [0401]).

6.3 Beside the particular amounts for the known components and the nature of the antibody (Trastuzumab instead of Pertuzumab), the claimed subject-matter differs notably from the formulations of D8 by:

(i) the presence of 2000 U/ml of the rHuPH20 hyaluronidase enzyme, and

(ii) the presence of 10mM methionine.

6.4 According to the patent in suit, the hyaluronidase component acts locally by enhancing the delivery of the active anti-HER2 antibody (cf. page 10). In addition, the respondent's case is based on the achievement of a technical effect, namely that the compositions are stable and ready-for-use, and the activity of both the antibody and the hyaluronidase are retained or improved by the presence of methionine.

A comparison of formulations X (page 41 of the patent in suit, according to claim 1, i.e. comprising methionine and 2000 U/ml rHuPH20) and composition G (page 28 of the patent in suit, comprising methionine but lacking the hyaluronidase enzyme) shows that the addition of the hyaluronidase enzyme does not lead to detrimental effects on the stability or formation of aggregates, as measured by size exclusion HPLC (see [0143]). The same absence of a significant effect on stability is apparent from a comparison of the data obtained in ion exchange chromatography for formulations G and X. Having regard to the Board's conclusion on the main request (see below), the question of whether this absence of a negative effect on stability is demonstrated to be caused by the presence of methionine can be left unanswered.

6.5 The problem to be solved may accordingly be regarded as the provision of alternative highly concentrated, stable anti-HER2 antibody pharmaceutical formulations that are ready for subcutaneous administration. The Board does not doubt that the subject-matter of claim 1 solves this problem over its whole scope, considering that claim 1 is essentially limited to formulation X with respect to its components and their respective amounts.

6.6 Starting from D8, and in order to arrive at the claimed anti-HER2 antibody formulation, the skilled person would *inter alia* have to modify the known formulation by incorporating, in their respective claimed amounts, not only the hyaluronidase enzyme but also methionine.

The skilled person may find in D1 an incentive for the addition of hyaluronidase: D1 discloses that hyaluronidase glycoproteins have the ability to open channels in the interstitial space thereby temporarily facilitating diffusion of molecules (cf. [0051]). Subcutaneous, intradermal and intramuscular administration of molecules in the presence of hyaluronidases thus facilitate their systemic distribution (cf. [0054]). A number of anti-cancer or chemotherapeutic agents can be combined with hyaluronidase by co-formulation or co-administration, including the anti-HER2 antibody Trastuzumab (cf. [0433]).

As to methionine, its presence in the formulation is considered in D8 (cf. [0384]), however as an antioxidant and without mention of an amount.

6.7 However the respondent has shown that the formulation of two enzymes together may be detrimental to the stability and activity of both proteins. Declaration D21 (including Exhibits 1 and 2) as well as D19 show that the skilled person would be aware of the importance of physicochemical properties of proteins when developing a formulation. As mentioned in D21-Exhibit 1 (cf. page 4, last paragraph), "these properties [...] should guide the choice of formulation components for testing in the initial screen of candidate formulations". As a result, the fact that, using the formulation defined in claim 1, the stability of the formulation is retained upon addition of the hyaluronidase enzyme (as demonstrated for formulation X) could not be foreseen on the basis of D8 and D1.

6.8 This could not be foreseen either taking D23 into account:

The claimed subject-matter is not entitled to priority from D24, since D24 does not disclose formulation X comprising 2000 U/ml rHuPH20. As a result, D23 is prior art pursuant to Article 54(2) EPC. D23 relates to an Herceptin (trastuzumab) formulation for subcutaneous injection, tested in phase 3 clinical trial, and delivered subcutaneously as a single premixed solution containing the hyaluronidase enzyme (cf. column 1 lines 1-16; column 3, lines 29-30). However, D23 is silent on the effect of the hyaluronidase enzyme on the stability of the formulation, and on the presence of methionine.

6.9 Accordingly, the main request meets the requirements of Article 56 EPC.

7. Sufficiency of disclosure

The appellant submitted that claim 1 of the main request as maintained by the opposition division lacks a sufficient disclosure as a result of its broadness. This argument is not applicable to the amended main request, which is essentially limited to formulation X. No demonstration was adduced that the claim covers formulations which are not suitable for subcutaneous administration. As to the achievement of the claimed effect of stability, for the Board, the term "stable" being left undefined, it suffices that a formulation exhibit any reasonable level of stability for the requirement of claim 1 to be met. This requirement is clearly met by formulation X considering the above reasoning on inventive step.

Accordingly the criteria of sufficiency of disclosure are met.

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 on the basis of the main request filed with letter dated 7 January 2019 and a description to be adapted.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated