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**Datasheet for the decision
of 24 October 2024**

Case Number: T 0810/22 - 3.3.07

Application Number: 12763896.3

Publication Number: 2691112

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A61P35/00, A61K39/00

Language of the proceedings: EN

Title of invention:
STABLE FORMULATIONS OF ANTIBODIES TO HUMAN PROGRAMMED DEATH
RECEPTOR PD-1 AND RELATED TREATMENTS

Patent Proprietor:
Merck Sharp & Dohme LLC

Opponents:
Strawman Limited
König Szynka Tilmann von Renesse

Headword:
Pembrolizumab formulation/MSD

Relevant legal provisions:
EPC Art. 84, 56

Keyword:

Claims - clarity (yes)

Inventive step - (yes)

Decisions cited:

T 0472/88



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Case Number: T 0810/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 24 October 2024

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
7 January 2022 concerning maintenance of the
European Patent No. 2691112 in amended form**

Composition of the Board:

Chairwoman J. Lécaillon
Members: J. Molina de Alba
 L. Basterreix

Summary of Facts and Submissions

- I. The decision under appeal is the opposition division's interlocutory decision concluding that European patent No. 2 691 112 as amended according to the main request filed on 13 March 2020, and the invention to which it relates, met the requirements of the EPC.

Claim 2 of the request held allowable by the opposition division read as follows:

"2. A stable liquid pharmaceutical formulation of an anti-human PD-1 antibody, comprising:

- a) 25 mg/mL of the anti-human PD-1 antibody in aqueous solution;*
- b) 70 mg/mL sucrose;*
- c) 0.2 mg/mL polysorbate 80; and*
- d) 10 mM histidine buffer at pH 5.0-6.0,*

wherein the antibody, comprises:

light chain comprising amino acid residues 20 to 237 of SEQ ID NO: 36 and a heavy chain comprising amino acid residues 20 to 466 of SEQ ID NO: 31."

- II. The decision under appeal refers, *inter alia*, to the following documents:

- D1 WO 2008/156712 A1
- D6 N.W. Warne, European Journal of Pharmaceutics and Biopharmaceutics, 2001, 78, 208-212
- D16 N.W. Warne, Formulation and Process Development Strategies for Manufacturing Biopharmaceuticals, Chapter 6, Willey, 2010, 147-159

D34 Sworn statement by C.N. Narasimhan dated
22 July 2019

- III. In the decision, the opposition division concluded, among other things, that the main request involved an inventive step starting from D1 as the closest prior art.
- IV. Opponent 2 (appellant) filed an appeal against the decision. In the statement of grounds of appeal, it requested that the decision be set aside and that the patent be revoked in its entirety.
- V. With its reply to the statement of grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed, implying that the patent be maintained in the version held allowable by the opposition division (then main request). In addition, the respondent maintained the eight auxiliary requests filed during the opposition proceedings with the letter dated 13 March 2020.
- VI. Opponent 1 (party as of right) did not make any substantive submissions or requests in these appeal proceedings.
- VII. The board scheduled oral proceedings and gave its preliminary opinion on the case.
- VIII. Oral proceedings were held before the board on 24 October 2024. During the oral proceedings, the respondent withdrew its then main request and auxiliary requests 1 to 5 and rendered auxiliary request 6 filed on 13 March 2020 its main request. This final main request contains a single independent claim which reads as follows (the features underlined by the board

indicate the limitations introduced compared with claim 2 of the request held allowable by the opposition division):

"1. A stable liquid pharmaceutical formulation of an anti-human PD-1 antibody for use in a method of treatment by therapy, wherein the formulation consists essentially of:

a) 25 mg/mL of the anti-human PD-1 antibody in aqueous solution;

b) 70 mg/mL sucrose;

c) 0.2 mg/mL polysorbate 80; and

d) 10 mM Histidine buffer at pH 5.5,

wherein the antibody is h409A11."

The antibody h409A11 is also known as pembrolizumab.

IX. At the end of the oral proceedings, the board announced its decision.

X. The appellant's arguments relevant to the present decision can be summarised as follows.

The expression "consists essentially of" rendered claim 1 unclear. The skilled person did not know which ingredients could be added in addition to those explicitly defined in claim 1 to give a formulation that could still be considered stable.

Document D1 was the closest prior art. The formulation of claim 1 differed from D1 in the combination of components a) to d). These differences produced the technical effect that the formulation was sufficiently stable for human administration in clinical trials. Therefore, in line with the decision under appeal, the

objective technical problem was to provide a stable formulation of pembrolizumab suitable for human use.

The solution proposed in claim 1 was obvious in light of the strategy proposed in D16 and D6 for finding stable antibody formulations suitable for early clinical trials. By applying the teaching of D16 and D6 to pembrolizumab, the skilled person would arrive at the formulation of claim 1 using routine tests. The fact that the formulation was not only suitable for early clinical trials but also for late trials and marketing was irrelevant. An enhanced effect could not render the claimed subject-matter inventive if it emerged from obvious tests; the enhanced stability of the formulation of claim 1 was merely a bonus effect (Case Law, tenth edn., 2022, I.D.9.21.7 and I.D.10.8).

XI. The respondent's arguments relevant to the present decision can be summarised as follows.

The expression "consists essentially of" had a clear meaning in accordance with the case law and did not render claim 1 unclear.

D1 was the closest prior art. The formulation of claim 1 differed from D1 in that it consisted essentially of components a) to d). The formulation of claim 1 was highly stable and could be used for human administration in late clinical trials and for marketing. It corresponded to the liquid product marketed as KeytrudaTM, which was stable for at least two years under refrigeration (D34, points 3 and 12). Therefore, the objective technical problem was to provide a formulation of pembrolizumab for human use which had optimised stability.

The skilled person would not look for the solution in D16 or D6 since these documents merely proposed a theory for the quick preparation of formulations having a stability sufficient for early clinical testing. The theory was not consistent with the data of commercial antibody formulations on which it was based and had never been confirmed. In addition, D16 and D6 acknowledged that finding a formulation with a stability suitable for marketing was beyond routine work. The skilled person had to carry out a research project with an uncertain outcome since it was not known whether there would be a formulation of pembrolizumab suitable for marketing.

XII. The parties' final requests were the following.

- The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.
- The respondent requested that the patent be maintained in amended form on the basis of the claims of the main request filed as auxiliary request 6 with the letter dated 13 March 2020.
- The party as of right did not make any request in these appeal proceedings.

Reasons for the Decision

1. The appellant did not object to the main request under Article 123(2) and (3) EPC. The board sees no reason to adopt a different position.
2. *Clarity (Article 84 EPC) - main request*
 - 2.1 Claim 1 is directed to a stable liquid pharmaceutical formulation of h409A11 (pembrolizumab) for use in a method of treatment by therapy. The formulation consists essentially of components a) to d). The parties disputed whether the expression "consists essentially of" renders claim 1 unclear.
 - 2.2 It was undisputed that, in accordance with established case law, the expression "consists essentially of" in claim 1 means that, in addition to components a) to d), the formulation may contain other components provided they do not materially affect the essential characteristics of the formulation (see e.g. T 472/88, Reasons 3). It was also undisputed that the essential characteristic of the formulation of claim 1 is stability. The appellant's clarity objection was instead that the skilled person could not ascertain from the wording of claim 1 alone which additional components were allowed by claim 1. This was allegedly even more the case considering that the claim did not define the meaning of the feature "stable".
 - 2.3 The board does not agree with the appellant's view.

With regard to the argument that the skilled person should know from the wording of claim 1 alone which additional components are allowed by claim 1, the board notes that this is not a requirement for clarity. It is common practice that claims contain functional features which do not render immediately apparent which structural features meet the required function. However, such features are not necessarily regarded as being unclear. This is the case, for instance, if the skilled person is able to ascertain by a routine test specified in the description or known to the skilled person whether a structural feature meets the function (see also Case Law, tenth edn., 2022, II.A.3.4).

In the current case, claim 1 is directed to a stable formulation for use in a method of treatment by therapy. Thus, claim 1 requires that the formulation is sufficiently stable for administration to patients.

In the discussion of inventive step across the opposition and subsequent appeal proceedings, the parties agreed that a liquid formulation composed of components a) to b) meets that stability requirement. On that basis, they considered that the objective technical problem solved was the provision of a stable formulation suitable for human use. The parties never called into question that the skilled person is able to assess by a routine test whether a formulation meets that stability requirement. It was implicitly acknowledged that the skilled person has no difficulty in determining whether a formulation containing components a) to d) and any additional component is in accordance with claim 1. This view is in line with the common general knowledge disclosed in D16, which was extensively discussed by the parties for inventive step. D16 proposes an approach for finding a stable

formulation suitable for early clinical trials based on routine testing.

Therefore, the board holds that claim 1 does not contravene Article 84 EPC.

3. *Inventive step (Article 56 EPC) - main request*

3.1 The patent is concerned with the provision of stable formulations of anti-human PD-1 antibodies, such as pembrolizumab, for therapeutic use (patent, paragraphs [0002], [0014], [0075] and [0076]). It was found that the liquid formulation defined in claim 1 was stable for at least two years when refrigerated (patent, paragraphs [0108] and [0109]). This formulation corresponds to the liquid product marketed as KeytrudaTM (D34, points 3 and 12).

3.2 The parties agreed that document D1 constitutes the closest prior art.

D1 is directed to the provision of anti-human PD-1 antibodies (page 6, first paragraph; claim 1). In Example 5, it discloses the preparation of several humanised anti-PD-1 antibodies, including pembrolizumab. The antibodies were tested for their ability to bind the PD-1 receptor and to inhibit PD-L1 and PD-L2 ligands (Table V). Subsequently, it was tested whether they enhanced human T-cell response to *Staphylococcus* Enterotoxin B (Figure 7). Pembrolizumab gave positive results in all tests. On page 32, lines 2 and 3, D1 generally proposes to formulate the antibodies as lyophilised powders, slurries, aqueous solutions or suspensions. However, the document does not disclose any formulation example apart from the unspecified solutions used in the tests of Example 5.

Thus, D1 deals with the preparation and the therapeutic use of anti-human PD-1 antibodies but not with their formulation as a stable form suitable for human use.

3.3 It was common ground that the formulation of claim 1 differs from the disclosure in D1 in that it consists essentially of:

- a) 25 mg/mL of pembrolizumab in aqueous solution
- b) 70 mg/mL sucrose
- c) 0.2 mg/mL polysorbate 80
- d) 10 mM histidine buffer at pH 5.5

3.4 The technical effect produced by these differences is that the formulation has the high degree of stability required for phase 3 clinical trials and marketing. As indicated in point 3.1 above, the formulation of claim 1 is marketed as KeytrudaTM and remains stable for at least two years when refrigerated (D34, points 3 and 12 and patent, paragraphs [0108] and [0109]).

3.5 Therefore, the objective technical problem solved by the subject-matter of claim 1 is to provide a formulation of pembrolizumab that can be marketed for human therapeutic use.

3.6 The parties' discussion on obviousness focused on the teaching of documents D16 and D6.

3.6.1 D16 is a chapter of a textbook on the formulation of biopharmaceuticals. As indicated in the title of the chapter, D16 proposes an approach for the efficient formulation of biopharmaceuticals in early phases of clinical development. The introduction of D16 refers to the low probability of candidate proteins becoming a

commercial product and the need to save resources in formulation at early stages of clinical development to the benefit of increasing the number of candidates that proceed to phase 1 clinical trials. Therefore, D16 proposes a strategy for rapidly finding a simple formulation which is sufficiently stable for early clinical trials and can be administered by different routes. This strategy postpones the optimisation of the formulation, which is costly in terms of time and effort, to a later clinical phase in which the initial safety profile, route of administration and competitive environment are better known.

The method proposed in D16 is based on the experience of formulators in the field of pharmaceutical antibodies and the composition of the commercially available antibody formulations disclosed in Table 6.1. It is a simple method that uses standard excipients which have been used previously in antibody formulations and are broadly accepted by the regulatory authorities (page 152, first paragraph, last sentence). As a first step, D16 suggests focusing on buffers that provide pH values between 5 and 7.5, preferably starting from a pH of 6.0 using a buffer of 10 to 20 mM histidine (page 148, last paragraph, and page 149, third paragraph). Subsequently, D16 recommends adding polysorbate 20 or polysorbate 80 at a concentration between 0.005 and 0.2% (page 149, fourth paragraph; page 151, first paragraph). Lastly, the document proposes the addition of a stabiliser to protect the protein during ultrafiltration, lyophilisation and freeze-thawing, in particular sucrose at 1 to 9%. Nevertheless, D16 warns that sucrose hydrolyses in liquid dosage forms with slightly acidic pH, even under refrigeration (page 152, second paragraph).

D6 is a review article published one year after D16 by the same author. It conveys the same teaching as D16, based on the updated list of commercially available antibody formulations disclosed in Table 1 (see D6, abstract and section 3). D6 proposes using trehalose instead of sucrose in slightly acidic liquid formulations to avoid hydrolysis (passage bridging pages 210 and 211).

3.6.2 The appellant argued that how antibody formulations were actually developed had to be taken into consideration for assessing inventive step. This implied that, at an early stage of clinical development, the skilled person would apply the teaching of D16 and D6 to pembrolizumab. By doing so, the skilled person would arrive at the formulation of claim 1 by routine testing. The fact that the formulation was not only suitable for early clinical trials but that its stability was high enough for marketing was merely an enhanced effect that could not justify the acknowledgement of an inventive step. The appellant referred to the case law holding that an enhanced effect cannot render the claimed subject-matter inventive if it emerges from obvious tests (Case Law, tenth edn., 2022, I.D.9.21.7 and I.D.10,8).

3.6.3 The board does not agree with that argument. There is no contradiction between how antibody formulations are developed and the consideration that the formulation of claim 1 is inventive. Furthermore, the case law cited by the appellant is not applicable to the circumstances of the case in hand.

The reality of the development of antibody formulations is reflected in D16 and D6, both of which constitute common general knowledge. They describe the situation

that only few of the candidates entering clinical development become commercial products and that, therefore, formulation efforts and resources need to be saved at early stages of clinical development. This can be done by applying systematic routine tests based on previous knowledge and experience which can lead to a formulation sufficiently stable for early clinical trials without investing too many resources. As mentioned in point 3.6.1 above, D16 and D6 propose first testing the stability of the antibody within a pH range of 5 to 7.5, preferably starting at a pH of 6.0 with a buffer of 10 to 20 mM histidine. Then, polysorbate 20 or polysorbate 80 can be titrated at concentrations between 0.005 and 0.2%. Lastly, a protecting agent is added which in lyophilised formulations is preferably sucrose but which in slightly acidic liquid formulations might need to be replaced by trehalose due to the tendency of sucrose to hydrolyse (D16, page 152, second paragraph; D6, paragraph bridging pages 210 and 211).

The skilled person applying the rationale of D16 and D6 to pembrolizumab could potentially arrive at different formulations with sufficient stability for early clinical trials by routine testing. It cannot be excluded that one of those formulations could be the one in claim 1. However, it can only be concluded with hindsight that, in a real situation, the skilled person quickly searching for a formulation suitable for early clinical trials would necessarily arrive at the formulation of claim 1 and that they would select that formulation from among other suitable formulations. This is even more the case considering that the formulation of claim 1 is not at the core of the teaching of D16 and D6, which propose to start testing liquid formulations at a pH value of 6.0 and to use

trehalose instead of sucrose. Therefore, the board concludes that the formulation of claim 1 is the result of an optimisation process for late clinical development and marketing rather than the outcome of a quick routine search for a formulation sufficiently stable for early clinical trials which, by chance, appeared to have an enhanced effect. As acknowledged by D16 and D6, such an optimisation process requires an amount of time and effort that goes beyond routine work.

3.7 Therefore, the main request involves an inventive step (Article 56 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 on the basis of the claims of the main request filed as auxiliary request 6 on 13 March 2020 and a description and figures to be adapted if necessary.

The Registrar:

The Chairwoman:



B. Atienza Vivancos

J. Lécaillon

Decision electronically authenticated