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Datasheet for the decision of 11 February 2020

Case Number: T 2342/16 - 3.3.07

Application Number: 06846683.8

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Language of the proceedings: EN

Title of invention:
STABLE PROTEIN FORMULATIONS

Patent Proprietor:
Bristol-Myers Squibb Company

Opponents:
D Young & Co LLP
Potter Clarkson LLP
ISENBRUCK BÖSL HÖRSCHLER LLP

Headword:
Stable protein formulations/BMS

Relevant legal provisions:
EPC Art. 123(2), 83, 56

Keyword:

Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

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Beschwerdekammern

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Case Number: T 2342/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 February 2020

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 12 August 2016 concerning maintenance of the European Patent No. 1962886 in amended form.**

Composition of the Board:

Chairwoman Y. Podbielski
Members: A. Usuelli
D. Boulois

Summary of Facts and Submissions

I. Three oppositions had been filed against European patent 1 962 886 on the grounds that its subject-matter extended beyond the content of the application as filed, was not sufficiently disclosed and lacked inventive step. The following documents were among those cited during the first-instance proceedings:

D1: WO 97/28267
D2: WO97/04801
D8: WO02/30463
D10: WO 02/02638
D20: Journal of Pharmaceutical Sciences, 93 (6), 1390-1402, 2004
D21: "Therapeutic peptides and proteins: formulation, processing, and delivery Systems" 2nd ed., November 2005, page 108
D22: WO 2005/072772
D28: International Journal of Pharmaceutics, 185, 129-188, 1999
D29: Drug Development Research, 61, 137-154,2004
D30: Pharmaceutical Research, 11(10), 1994, S-72
D37: "Rational Design of Stable Protein Formulations: Theory and Practice", 2002, pages 177, 182-183 and 187-188
D39: Second declaration of Charles Dahlheim, 1 June 2016

II. The opposition division held that the patent and the invention to which it related according to auxiliary request 3 met the requirements of the EPC. The decision was based on the main request and three auxiliary requests filed on 3 June 2016.

This decision was appealed by the patent-proprietor (hereinafter "the appellant"). An appeal was filed also by opponent 2 but it was subsequently withdrawn.

III. Claim 1 of the main request forming part of the basis of the opposition division's decision read as follows:

"1. A formulation suitable for subcutaneous administration comprising 125 mg/ml CTLA4Ig molecules, a sugar selected from the group consisting of sucrose, lactose, maltose, mannitol and trehalose and mixtures thereof, and a pharmaceutically acceptable aqueous carrier, wherein the formulation has a pH range of from 6 to 8 and a viscosity of from 9 to 20 mPa·s, and the weight ratio of sugar:protein is 1.1:1 or higher".

Claim 1 of the request considered by the opposition division to comply with the requirements of the EPC (auxiliary request 3) read as follows:

"1. A formulation suitable for subcutaneous administration comprising 125 mg/ml CTLA4Ig molecules, sucrose, and a pharmaceutically acceptable aqueous carrier, wherein the formulation has a pH range of from 6 to 8 and a viscosity of from 9 to 20 mPa·s, and the weight ratio of sucrose:protein is 1.1:1 or higher, and the CTLA4Ig molecule has the amino acid sequence shown in Figure 1 starting at methionine at position 27 or alanine at position 26 and ending at lysine at position 383 or glycine at position 382."

IV. The opposition division held that the combination of the list of sugars with the concentration of CTLA4Ig recited in claim 1 of the main request could not be derived directly and unambiguously from the original application. Hence, the main request did not comply

with the requirements of Article 123(2) EPC. Claim 1 of auxiliary requests 1 and 2 did not comply with Article 123(2) EPC essentially for the same reasons given in respect of the main request.

Auxiliary request 3 was considered by the opposition division to comply with the requirements of Articles 123(2), (3) and 84 EPC. Documents D1, D10 and D30 were regarded as suitable starting points for the assessment of inventive step. The subject-matter of claim 1 differed from the disclosures of these documents in the specific components of the formulation. The objective technical problem was the provision of a stable CTLA4Ig formulation suitable for subcutaneous administration. In the opposition division's view, the results disclosed in the prior art documents in relation to formulations containing specific proteins could not be extrapolated to formulations containing other proteins such as CTLA4Ig. Hence, the skilled person confronted with the problem of providing a stable CTLA4Ig formulation would have been obliged to start an extensive research program without reasonable expectation of success. Accordingly, claim 1 of auxiliary request 3 met the requirements of Article 56 EPC.

The protein concentration, the sucrose:protein ratio, the pH and the viscosity could be determined by routine methods. Hence, the subject-matter of auxiliary request 3 was sufficiently disclosed.

V. With the statement setting out the grounds of appeal filed on 22 December 2016 the appellant requested that the decision of the opposition division be set aside and a patent be maintained on the basis of the main request filed during the first instance proceedings on

3 June 2016 or alternatively on the basis of one of the auxiliary requests filed at the same date.

VI. In a communication pursuant to Article 15(1) RPBA 2007 the Board agreed with the appellant in considering that the combination in claim 1 of the main request of the list of sugars with the feature "comprising 125 mg/ml CTLA4Ig" did not offend against Article 123(2) EPC. With regard to the requirement of sufficiency of disclosure it expressed the view that the objections raised by the opponents (respondents) were unconvincing. As to the assessment of inventive step the Board stated that it agreed with the appellant in considering D30 as the closest prior art.

VII. Oral proceedings were held on 11 February 2020. They were attended only by the appellant. Respondent 1 and respondent 3 had informed the Board in advance that they would not attend. The Board had received no such information from respondent 2.

VIII. The appellant's arguments can be summarised as follows:

(a) The skilled person would have read the list of sugars disclosed in original claim 2 in combination with paragraphs [0023] and [00119] of the application as filed which referred to a CTLA4Ig concentration of 125 mg/ml. Hence, claim 1 of the main request met the requirements of Article 123(2) EPC.

(b) The respondent had not provided any evidence to support its position that it would be implausible to prepare a formulation with a viscosity of only 9 mPa·s, as required by claim 1. Thus, the main

request met the requirements of sufficiency of disclosure.

(c) Document D30 provided some information regarding degradation pathways of a liquid CTLA4Ig formulation containing a phosphate buffer. This document was the more realistic starting point for the assessment of inventive step. The technical problem was the provision of a liquid CTLA4Ig formulation that was ready to be administered subcutaneously and had a sufficient long-term stability. Formulating a stable liquid protein composition was a challenge due to the different chemical and physical properties of the proteins. The skilled person would not have expected different proteins to be similarly stable in the same formulation. Accordingly, he would not have considered the teaching of certain documents such as D20, D21, D28 and D37 since they did not concern CTLA4Ig molecules. In fact the prior art publications about CTLA4Ig, such as D10, taught away from the preparation of liquid protein formulation. Thus, the subject-matter of the main request met the requirements of inventive step.

IX. The respondents' arguments can be summarised as follows:

(a) There was no disclosure in the original application that lactose, maltose, mannitol, trehalose or mixtures thereof were present in a formulation comprising 125 mg/ml CTLA4Ig. There was also no disclosure for the combination of a viscosity of 9 to 20 mPa·s with a pH of 6 to 8 as required by claim 1, or a pH of 6 to 7.8 as required by claim 5, and for the combination of the viscosity with

the feature defining the sugar:protein ratio. Moreover, the original application did not provide any valid basis for a formulation containing Poloxamer 188 in an amount of about 8 mg/ml (claim 10) and having a pH from 6 to 8. For these reasons the main request did not comply with Article 123(2) EPC.

(b) It was implausible that a formulation containing CTLA4Ig in a concentration of 125 mg/ml and a sugar:protein ratio as defined in claim 1 could have a viscosity as low as 9 mPa.s. Thus, the main request was not sufficiently disclosed.

(c) Document D10 was the closest prior art. This document disclosed in example 3 that doses of 2 and 10 mg/kg were effective. D10 did not disclose any specific formulation of CTLA4Ig suitable for subcutaneous administration. The technical problem was the provision of an alternative CTLA4Ig formulation suitable for subcutaneous administration. The claims did not contain any restriction regarding stability or storage time. Thus, the opposition division was erroneous in considering the stability of the formulation in the definition of the technical problem. Several documents, such as D2, D8, D20 and D29, suggested using high concentrations of sugars to stabilise liquid formulations containing protein. D28 and D37 specifically suggested the use of sucrose or trehalose as stabilisers. D2 taught using sugar:protein molar ratios falling within claim 1. Therefore, the subject-matter of claim 1 of the main request did not comply with the requirements of Article 56 EPC.

X. The appellant requested that the decision of the opposition division be set aside and a patent be maintained on the basis of the main request filed during the first instance proceedings on 3 June 2016 or alternatively on the basis of one of the nine auxiliary requests filed on the same date.

XI. Respondents 2 and 3 requested in writing that the decision under appeal be set aside and the patent be revoked. In view of the principle prohibiting *reformatio in peius* the Board interpreted these requests as asking that the appeal be dismissed. Respondent 1 had filed no request in the appeal proceedings.

Reasons for the Decision

Main request

1. Article 123(2) EPC

1.1 The opposition division considered that the combination of the feature "a sugar selected from the group consisting of sucrose, lactose, maltose, mannitol and trehalose" with the feature "comprising 125 mg/ml CTLA4Ig" had no basis in the original application. In this regard it observed that the list of sugars was disclosed in original claim 2 that referred back to claim 1. However, the latter was limited to a concentration of 100 mg/ml of CTLA4Ig whereas claim 1 of the main request recited a concentration of 125 mg/ml of CTLA4Ig. Thus, in the opposition division's view, the inclusion of the list of sugars in the context of a claim relating to a formulation with a different concentration of active ingredient did not

comply with Article 123(2) EPC. This conclusion is substantially endorsed by the respondents.

1.2 The Board notes that original claim 1 refers to a concentration of "at least 100 mg/ml" of CTLA4Ig (emphasis added). A concentration of at least 100 mg/ml covers also a concentration of 125 mg/ml. The specific concentration of 125 mg/ml is mentioned for instance in paragraph [00119] of the original application. This passage indicates that preferably the subcutaneous formulation comprises a CTLA4Ig concentration of at least 125 mg/ml in combination with a sugar. Although in the continuation of the paragraph it is stated that the sugar is preferably a disaccharide, the most general embodiment of paragraph [00119] relates to any sugar and therefore also to the sugars disclosed in original claim 2. Thus, the Board concurs with the appellant that the combination of the list of sugars with the feature "comprising 125 mg/ml CTLA4Ig" does not offend against Article 123(2) EPC.

1.3 Paragraph [00119] of the original application also discloses the ratio of sugar to protein recited in claim 1 of the main request. The pH and viscosity intervals recited in claim 1 of the main request are disclosed respectively in paragraphs [00127] and [00139] of the original application. Both paragraphs relates in general to subcutaneous CTLA4Ig formulations and do not provide any restriction as to the other components of the formulation.

Thus, the introduction in original claim 1 of the features defining the sugar to protein ratio, the pH and the viscosity does not result in addition of subject-matter.

1.4 Accordingly, claim 1 of the main request complies with the requirements of Article 123(2) EPC.

1.5 Paragraph [00127] of the original application also indicates that the pH of the subcutaneous formulation is preferably 6 to 7.8, as recited in claim 5 of the main request. Several passages of the original application, such as paragraphs [00133], [00235], [00241] and claim 17 refer to subcutaneous formulations containing Poloxamer 188 in an amount of 8 mg/ml as required by claim 10 of the main request. There is also no indication in the original application that the use of Poloxamer 188 is limited to formulations having any specific value of pH. Thus, the objections raised by the respondents pursuant to Article 123(2) EPC in relation to claims 5 and 10 are not convincing.

1.6 On account of the considerations set out above, the Board concludes that the main request complies with the requirements of Article 123(2) EPC.

2. Sufficiency of disclosure

2.1 Respondents 2 and 3 observe that the formulation disclosed in Table 5 of the patent, containing 125 mg/ml of CTLA4Ig, 170 mg of sucrose and a sugar/protein ratio of 1.36:1, has a viscosity of 13±2 mPa·s. In their opinion, in view of this high value of viscosity it would be implausible that a formulation containing 125 mg/ml of CTLA4Ig could have a viscosity as low as 9 mPa·s, as required by claim 1 of the patent.

2.2 In the Board's view, this objection is unfounded and the reasoning behind it is unconvincing for the following reasons. Claim 1 of the main request covers

formulations containing less sugar than the formulation of Table 5 because the minimum value for the sugar/ protein ratio is 1.1:1. Accordingly, since the amount of CTLA4Ig in the formulation of claim 1 is 125 mg/ml, the minimum amount of sugar is 137 mg/ml (i.e. 125 X 1.1). This amount is well below the amount of 170 mg/ml of the formulation of Table 5. A formulation containing less sugar is expected to have a lower viscosity. Thus, on the basis of the viscosity value of the formulation of Table 5 it cannot be concluded that a viscosity of 9 mPa·s cannot be achieved.

2.3 Therefore, the Board concludes that the main request complies with the requirements of sufficiency of disclosure.

3. Inventive step

3.1 Closest prior art

3.1.1 Claim 1 of the main request relates to a an aqueous formulation of CTLA4Ig molecules in a concentration of 125 mg/ml, said formulation being suitable for administration via a subcutaneous route. The term "CTLA4Ig molecules" refers to a family of proteins useful in the treatment of immune system diseases.

In the description of the patent it is explained that formulating liquid compositions of highly concentrated proteins is particularly challenging due the tendency of the proteins to aggregate ([0003]). Aggregation is the primary degradation pathway of the protein solution and may affect their activity, pharmacokinetics and safety ([0005]). Thus, the invention underlying the main request aims at providing a stable liquid formulation of CTLA4Ig molecules suitable for

subcutaneous administration. "Stable" means that the CTLA4Ig molecules essentially retain the physical and chemical stability and integrity upon storage ([0030]).

3.1.2 The appellant considers D30 as the closest prior art whereas in the respondents' opinion D10 should be taken as the starting point for the assessment of inventive step. In this regard, the Board observes the following.

Document D30 addresses the issue of lack of stability of the CTLA4Ig proteins in solutions and indicates that aggregation is the predominant pathway of degradation. This document briefly refers to aqueous solutions of CTLA4Ig in phosphate buffer at pH 8.

Document D10 relates to methods for treating rheumatic diseases by administering to a subject an effective amount of CTLA4 molecules (page 1, lines 16 to 20). In the paragraph bridging pages 31 and 32, D10 gives generic information as to the pharmaceutical compositions suitable for achieving the therapeutic purpose by providing a list of suitable carriers and adjuvant. However, no specific CTLA4Ig formulation is disclosed in D10 and no discussion is made in this document as to the issue of stability of the formulations, not to mention the specific issue of providing stabile aqueous formulations of CTLA4Ig molecules suitable for subcutaneous administration. The respondents referred in particular to example 3 of D10 as a more realistic starting point for assessing inventive step than the formulation of D30. This example discloses a phase II clinical study concerning the use of CTLA4Ig molecules in the treatment of symptoms associated with rheumatoid arthritis. As explained on page 61, line 29, the CTLA4Ig formulation is administered intravenously. Claim 1 of the main

request relates instead to a formulation for subcutaneous administration. Moreover, example 3 of D10 explains that CTLA4Ig is supplied in single-use vials and is diluted, prior to infusion, to a final concentration of 25 mg/ml with sterile water for injection (page 61, lines 22-25). Thus, the formulation administered to the patients is a liquid formulation prepared before the use. This is in line with the general indications reported on page 35 of D10 (lines 19-21), where it is explained that the therapeutic agent is commonly lyophilised for storage and reconstituted prior to administration. Thus, the liquid formulation administered to the patient does not need to be storage stable since it is used immediately after its preparation. Example 3 does not provide any detailed information about the CTLA4Ig composition supplied in single-use vials. However, in the light of the information disclosed on page 35, this is very likely a lyophilised product.

In the Board's view, a formulation that is not conceived to be stable cannot be regarded as a realistic starting point of a research project whose scope is to provide a stable liquid formulation. Thus, D10 is not a realistic starting point for the assessment of inventive step.

3.1.3 For the above reasons the Board agrees with the appellant that document D30 is the closest prior art.

The subject-matter of claim 1 of the main request differs from the disclosure of D30 in the specific definition of the formulation, namely in the indication of the concentration of the CTLA4Ig molecules, in the presence of a sugar, and in the indication of the viscosity.

3.2 Technical problem

3.2.1 The patent provides several data on the stability of liquid formulations containing CTLA4Ig molecules. Particularly relevant in the context of defining the technical problem are those data concerning formulations wherein the concentration of CTLA4Ig is 125 mg/ml, as in claim 1 of the main request. Such data are disclosed for instance in Tables 18 and 28 of the patent. They concern the stability of formulations according to claim 1 upon storage at 2-8°C, or 25°C and 60% RH. As noted by the respondents, in some cases the increase of high molecular weight species (HMWS), i.e. the increase of CTLA4Ig multimers deriving from processes of aggregation, is above the desired upper limit disclosed in paragraph [0030] (5% after one year for a formulation stored at 2-8°C). Nevertheless, Table 28 indicates that even after 9 months of storage at 2-8°C the total amount of HMWS is below 2%. Furthermore, in his declaration of 1 June 2016 (D39), Mr Dahlheim explains that, on the basis of stability studies conducted over the temperature range of 5°C to 35°C, a shelf life at 2-8°C of more than one year could be predicted. In paragraph 10 of his declaration, he further indicates that a formulation for subcutaneous administration is currently commercialised in pre-filled syringes containing 125 mg of abatacept (CTLA4Ig) as a solution with a pH of 6.8 to 7.4 and a shelf life of 2 years when stored at 2-8°C.

3.2.2 In the respondents' view, the effect of stability of the formulations should be disregarded in the assessment of inventive step since the claims contain no restriction regarding stability. The Board cannot share this conclusion.

The formulation of the technical problem is based on the technical effects provided by the invention over the closest prior art. However, there is no requirement that a certain technical effect be recited in a claim in order to be considered for the definition of the technical problem and therefore for the assessment of inventive step.

3.2.3 On the basis of the evidence discussed in point 3.2.1 above, the Board, in agreement with the decision under appeal, defines the technical problem as the provision of a stable CTLA4Ig formulation suitable for subcutaneous administration.

3.3 Obviousness

3.3.1 In the respondents' view it was part of the common general knowledge of the skilled person to use sugars, in particular sucrose and trehalose, in order to stabilise liquid formulations of proteins. In this regard they referred to several documents such as D2, D8, D20 to D22, D28 and D37.

3.3.2 The Board notes in this respect, that none of the documents referred to by the respondents relates to liquid formulations of CTLA4Ig molecules. Moreover, some of these documents warn against the possibility of making speculative extrapolations valid for the entire class of proteins. Thus, D28 indicates that "...the structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful..." (page 130, last sentence) and "...there is still no single pathway to follow in formulating proteins due to their structural diversities and

complexities..." (page 175, left-hand column, second paragraph). At the same time, the prior art acknowledges the difficulties associated with the preparation of a stable liquid formulation of a protein. D37 reports that "...most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed..." (page 188, lines 12 to 14). In line with this, the authors of D30 conclude that the stability of aqueous solutions of CTLA4Ig "is not sufficient for long-term storage". As a matter of fact there is no prior art document disclosing a liquid formulation of CTLA4Ig, which would be suitable for long term stability.

In addition to the above considerations, the Board notes that there is no teaching in the prior art as to the weight ratio of sugar to CTLA4Ig, the viscosity of the formulation and the CTLA4Ig concentration.

It follows that starting from document D30, the skilled person would not arrive at the subject-matter of claim 1 in an obvious manner.

3.4 As explained in point 3.1 above, the D10 does not qualify as a suitable starting point for the assessment of inventive step. In any case, the conclusion set out in point 3.3.2 above would hold good also if D10 were selected as the closest prior art. Indeed D10 does not disclose any specific formulation of CTLA4Ig. In this regard it is observed that example 3 does not provide any detailed information about the composition of the product supplied in single-use vials which is then diluted before administration (see point 3.1.2 above). Hence, the skilled person would have to start his work from the very generic information provided in the paragraph bridging pages 31 and 32 of D10. Furthermore,

the considerations made in paragraph 3.3.2 above would still apply in particular the observation that there is no prior art document disclosing a liquid formulation of CTLA4Ig suitable for long term stability.

Hence, the subject-matter of claim 1 would be inventive also when starting from D10 as the closest prior art.

3.5 Thus, the main request complies with the requirements of 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 a patent on the basis of the main request filed on 3 June 2016 and a description to be adapted thereto.

The Registrar: The Chairwoman:

B. Atienza Vivancos Y. Podbielski

Decision electronically authenticated