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Title of invention:
Antibody-containing solution pharmaceuticals

Applicant:
Chugai Seiyaku Kabushiki Kaisha

Headword:
Solution pharmaceuticals/CHUGAI SEIYAKU KABUSHIKI KAISHA

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request - inventive step (no)"
"First auxiliary request - inventive step (yes)"

Decisions cited:
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Catchword:
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Case Number: T 0028/09 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 18 June 2013

Appellant: (Applicant)
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 22 July 2008 refusing European patent application No. 03705165.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: B. Claes
G. Alt

Summary of Facts and Submissions

I. The appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse European patent application 03705165.3 with the title "*Antibody-containing solution pharmaceuticals*" which was published as international application WO 2003/068259.

II. The examining division decided that the subject-matter of claims 1 to 12 of the sole (main) request before it, which was filed with a letter dated 12 October 2007, lacked an inventive step (Article 56 EPC). During the oral proceedings before the examining division on 22 October 2007 the applicant had filed a first auxiliary request. On 26 November 2011 the examining division issued a communication pursuant to Rule 51(4) EPC 1973 in respect of this first auxiliary request and giving reasons for the refusal of the main request. With a letter dated 3 April 2008 the applicant disapproved the text of the first auxiliary request and maintained solely the main request.

Independent claim 1 of the sole (main) request read:

"1. An antibody-containing solution formulation comprising acetic acid and a surfactant as stabilizers, wherein the antibody is an anti-interleukin-6 receptor antibody or an anti-HM1.24 antigen antibody and wherein the concentration of acetic acid is in the range of 5 to 100 mM."

Independent claim 1 of the withdrawn first auxiliary request read:

"1. Use of 5 to 100 mM acetic acid for suppressing formation of visible insoluble matter and/or insoluble particles caused by Fe ions present in an antibody-containing solution formulation, which comprises a surfactant as a stabilizer and an anti-HM1.24 antigen antibody of IgG1 class as an antibody."

Claims 2 to 8 of this request were dependent on claim 1.

III. With the statement of the grounds of appeal dated 1 December 2008 the appellant filed a main request, which was identical to the sole (main) request before the examining division (see section II), and two auxiliary requests. The appellant filed a new test report and argued in favour of inventive step of the subject-matter of claim 1 of the main request.

IV. After having been summoned to oral proceedings, the appellant filed with a letter of 17 May 2013 a new set of seven auxiliary requests.

Claim 1 of the first auxiliary request read:

"1. Use of acetic acid for suppressing formation of visible insoluble matter and/or insoluble particles caused by Fe ions present in an antibody-containing solution formulation, wherein the antibody-containing solution formulation comprises the acetic acid and a surfactant as stabilizers, wherein the antibody is an anti-interleukin-6 receptor antibody or an anti-HM1.24 antigen antibody and wherein the concentration of acetic acid is in the range of 5 to 100 mM."

Claims 2 to 11 of this request were dependent on claim 1.

V. Oral proceedings were held on 18 June 2013. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or one of the first to seventh auxiliary requests, all filed with its letter of 17 May 2013.

VI. The following documents are further referred to in the present decision:

D1: EP-A-1174148

D2: US6252055

D3: W098/56418

D4: W098/22136

D5: EP-A-0628639

D6: EP-A-0628643

VII. The appellant's arguments, insofar as they are relevant for the present decision, can be summarised as follows:

Main request - claim 1 - inventive step
(Article 56 EPC)

Claim 1 referred to a solution formulation which contained an anti-IL-6 receptor antibody or an anti-HM 1.24 antigen antibody and which had reduced formation of visible insoluble matter and/or insoluble particles caused by Fe ions.

Document (D3) neither mentioned the specific antibodies nor the issue of aggregation due to Fe ions. The closest prior art was therefore either a document related to the specific antibodies, such as documents (D5) or (D6), or a document which mentioned the problem of aggregation due to Fe ions.

In view of the disclosure in either of documents (D5) or (D6), the objective technical problem was to provide a solution formulation which contained an anti-TL-6 receptor antibody or an anti-HM1.24 antigen antibody which had reduced formation of visible insoluble matter and/or insoluble particles caused by Fe ions.

The cited prior art did not disclose that visible insoluble matter and/or insoluble particles could be formed due to the presence of Fe ions or more particularly that their formation can be avoided by using acetic acid in a concentration of 5 to 100 mM. Consequently, it could not render the claimed subject-matter obvious.

Document (D3) related to certain aqueous pharmaceutical formulations comprising a therapeutically effective amount of an antibody, a buffer maintaining the pH in

the range from about 4.5 to about 6.0, a surfactant and a polyol (see claim 1). Acetate was used as buffer (see claim 16). There was no indication in this reference that acetic acid was suitable for suppressing the formation of visible insoluble matter and/or insoluble particles caused by Fe ions present in the solution. Furthermore, document (D3) did not consider any up-scaling of the production process, so that it envisaged using glass lab-ware, rather than the metal (Fe containing) containers of the invention.

According to the established case law of the Boards of Appeal a product claim had to include all of the features which were necessary to solve the objective technical problem. It was not necessary for the technical problem to be recited in a product claim. However, even if the intended use was not mentioned in the claim it had, of course, to be taken into account when assessing inventive step. Therefore, although claim 1 did not recite that the solution formulation is "for suppressing formation of visible insoluble matter and/or insoluble particles caused by Fe ions" this object could be taken into account because the means to overcome this problem (i.e. the presence of 5 to 100 mM acetic acid) were recited in the claim.

First auxiliary request - inventive step (Article 56 EPC)

None of the documents on file taught or suggested that 5 to 100 mM acetic acid could be used for suppressing formation of visible insoluble matter and/or insoluble particles caused by Fe ions present in the antibody-containing solution formulation. Rather acetate or

acetic acid was just mentioned as a possible buffer in the prior art (see document (D1), page 3, lines 47 to 51; document (D2), col. 3, lines 49 to 58; document (D3), page 22, lines 18 to 25; document (D4), page 9, lines 15 to 19). Following the principles set out in decision G 2/88, inventive step for the subject-matter of claim 1 of the first auxiliary request should be accepted.

Reasons for the Decision

1. The appeal is admissible.

Main request - claim 1 - inventive step (Article 56 EPC)

2. Claim 1 is to a product, i.e. an antibody-containing solution formulation wherein the antibody is an anti-interleukin-6 receptor antibody or an anti-HM1.24 antigen antibody. The product is defined to comprise acetic acid, in a concentration in the range of 5 to 100 mM, and a surfactant as stabilizers.

3. The application as published states that "[t]*he present invention relates to stable solution formulations containing antibodies*" (see paragraph [0001]) and similarly that storage conditions are necessary to ensure a stable supply of the antibodies (see paragraph [0002]). As the background of the invention in paragraph [0003] it is stated that "[w]*hen proteins are stored in a highly concentrated solution form, they are usually associated with a problem of deterioration, including the formation of insoluble aggregates, which is required to be prevented*". In paragraph [0005] it is

furthermore stated that "[t]*here is also a problem that visible insoluble matter and insoluble particles are formed in the presence of metal ions (Fe ions) introduced during the production process*". As a general aim of the invention it is then indicated in paragraph [0008] that "[e]*specially, there has been a need for* ***stable*** *solution formulations containing antibodies*" (emphasis added).

Closest prior art

4. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art.

5. Whereas the examining division, in the appealed decision, considered document (D3) to represent the closest prior art, the appellant considered rather the teaching of documents (D5) or (D6) to constitute the closest prior art (document (D5) for the anti-HM1.24 antigen antibody and document (D6) for the subject-matter related to the anti-interleukin-6 receptor antibody related subject-matter).

6. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention (see Chapter I.D.3

of the Case Law of the Boards of Appeal of the EPO, 6th Edition, 2010).

7. Documents (D5) and (D6) deal with the construction and expression of reshaped human antibodies as contained in the solution formulation of claim 1 (see point 4, above) and the *in vitro* evaluation of their antigen binding activity and binding inhibition activity. The documents are silent on the provision of stable solutions of the antibodies.

8. Document (D3) concerns a **stable** aqueous pharmaceutical formulation of an antibody, a buffer maintaining the pH in the range from about 4.5 to about 6.0, a surfactant and a polyol (see claim 1). Acetate is exemplified as a buffer (see claim 16) in a concentration of 5 to 30 mM (see claim 17). Document (D3) defines a "stable" formulation as one "*in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage*" (see page 5, lines 36 to 37). It is further stated that "[a] *protein "retains its physical stability" in a pharmaceutical formulation if it shows no signs of aggregation, precipitation and/or denaturation upon visual examination of color and/or clarity or as measured by UV light scattering or by size exclusion chromatography*" (see page 6, lines 5 to 7).

9. The appellant has argued that a product claim included all of the features which were necessary to solve the objective technical problem, which in themselves had not necessarily to be recited in the product claim. Accordingly, the intended use of a product had to be

taken into account when assessing inventive step. Therefore, although claim 1 did not recite that the solution formulation was "for suppressing formation of visible insoluble matter and/or insoluble particles caused by Fe ions" this purpose or effect should be taken into account when assessing inventive step because means to overcome this problem, i.e. the use of acetic acid in a particular concentration, were recited in the claim. The purpose or objective of the present invention was thus the suppression of the formation of visible insoluble matter and/or insoluble particles caused by Fe ions in antibody preparations and not to provide a stable antibody solution. Accordingly, either document (D5) or (D6) represented the closest prior art.

10. The board notes, however, that, even if the appellant's view of the purpose of the invention was accepted, documents (D5) and (D6) would not qualify as closest prior art since neither of them is concerned with the absence or presence of Fe ions or visible insoluble matter. Therefore, neither of them could be considered as matching the criteria to be fulfilled by closest prior art as reviewed in point 6 above.

11. Accordingly, in view of the above considerations, the teaching in document (D3) is conceived for the same purpose and aiming at the same objective as the claimed invention defined in claim 1 (see point 3, above). Therefore, in line with the established criteria, the board considers that, rather than the disclosures in documents (D5) and (D6), document (D3) represents the closest prior art.

The objective technical problem to be solved

12. The only technical difference between the formulations disclosed in document (D3) (see point 8 above) and the claimed formulation is the nature of the antibody. Accordingly, the board can agree with the examining division that the objective technical problem to be solved by the claimed invention is the provision of a stable antibody solution formulation wherein the antibody is directed to a different antigen.

13. In view of the experiments disclosed in the application for the anti-HM1.24 antigen antibody and the additional experimental data provided by the appellant with the statement of grounds of appeal, which show that acetic acid is effective in suppressing the formation of visible insoluble matter and/or insoluble particles caused by Fe ions in a solution formulation containing an anti-IL-6 receptor antibody, the board is satisfied that the subject-matter of claim 1 solves this problem.

Obviousness

14. Document (D3) provides stable pharmaceutical formulations containing protein in general without thereby being restricted to antibodies, let alone specific antibodies. The appellant has not argued that there existed particular reservations in the prior art to apply the acetate containing solution formulations of document (D3) to the antibodies as disclosed in documents (D5) and/or (D6). Accordingly, the board concludes that the skilled person would apply, in an obvious manner, the formulations of document (D3) in

combination with the anti-HM1.24 antigen antibody and the anti-interleukin-6 receptor antibody.

15. In view of the above considerations, the subject-matter of claim 1 of the main request lacks inventive step (Article 56 EPC).

First auxiliary request

16. This request contains a slight change in format from the first auxiliary request before examining division, in that claim 1 now reads: "*use of acetic acid for suppressing .... wherein the concentration of acetic acid is in the range of 5 to 100 mM*", compared to: "*Use of 5 to 100 mM acetic acid for suppressing ...*" (see section II above). However, the main difference between present claim 1 and claim 1 of the first auxiliary request filed during the oral proceedings before the examining division is that subject-matter related to anti-interleukin-6 receptor antibody has been reintroduced and the antibody class has been omitted from the definition.

17. The examining division had questioned in its decision whether the reinstated subject-matter in fact solved the technical problem. It had answered this question in the negative because the application lacked experimentation in this respect. The appellant has now filed further experimental data with the grounds of appeal which satisfy the board that acetic acid is effective in suppressing the formation of visible insoluble matter and/or insoluble particles caused by Fe ions in a solution formulation containing an anti-IL-6 receptor antibody (see point 13, above).

18. It appears from points 1.7 and 1.8 of the decision under appeal that the examining division was of the opinion that the auxiliary request filed during the oral proceedings before it complied with the requirements of the EPC. In view of the correspondence of present auxiliary request 1 and the auxiliary request before the examining division and its finding on *inter alia* inventive step, the board has no further objections to auxiliary request 1 which complies 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 department of first instance with the order to grant a patent on the basis of claims 1 to 11 of the first auxiliary request filed with the appellant's letter of 17 May 2013 and a description to be adapted thereto.

The Registrar The Chairman

P. Cremona C. Rennie-Smith