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Datasheet for the decision of 9 June 2022

Case Number: T 0654/21 - 3.3.07

Application Number: 15724974.9

Publication Number: 3148510

IPC: A61K9/00, A61K38/00, A61K47/18, A61K47/26

Language of the proceedings: EN

Title of invention:
LIQUID PHARMACEUTICAL COMPOSITION

Patent Proprietor:
Fresenius Kabi Deutschland GmbH

Opponents:
Biogen Inc.
Samsung Bioepis UK Limited

Headword:
Liquid adalimumab composition / FRESENIUS

Relevant legal provisions:
EPC Art. 100(c), 123(2)

Keyword:
Grounds for opposition - added subject-matter (yes) - combination of selected features
Amendments - allowable (no)

Decisions cited:
T 0524/17, T 1919/11

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Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0654/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 June 2022

Appellant: (Patent Proprietor)	Fresenius Kabi Deutschland GmbH Else-Kröner-Strasse 1 61352 Bad Homburg (DE)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent: (Opponent 1)	Biogen Inc. 225 Binney Street Cambridge, MA 02142 (US)
Representative:	Patent Boutique LLP 10A Printing House Yard Hackney Road London E2 7PR (GB)
Respondent: (Opponent 2)	Samsung Bioepis UK Limited 950 Great West Road Brentford Middlesex TW8 9ES (GB)
Representative:	Patent Boutique LLP 10A Printing House Yard Hackney Road London E2 7PR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 May 2021 revoking European patent No. 3148510 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 3 148 510 ("the patent") was granted on the basis of fourteen claims.

Independent claim 1 as granted related to:

"An aqueous pharmaceutical composition comprising:
(a) adalimumab;
(b) histidine buffering agent (or histidine buffer system);
(c) sugar stabiliser is selected from the group including trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; and
(d) 0.05 mg/mL to 2 mg/mL surfactant selected from Polysorbate 20 and Polysorbate 80;
wherein the composition:
• has a pH between 5.0 and 6.7;
• is either free of amino acids other than histidine or comprises one or more amino acids other than histidine in a (collective) concentration of at most 0.1 mM; and
• is either free of phosphate buffering agents or comprises a phosphate buffer system in a concentration of at most 0.1 mM."

II. Two oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed (European patent application 15724974.9, originally published as WO2015/177058).

III. The appeal was filed by the patent proprietor against the decision of the opposition division to revoke the patent. The decision was based on a main request relating to the patent as granted and auxiliary requests 1-7 filed on 3 March 2021.

The opposition division arrived at the following conclusions:

(a) Claim 1 as granted combined the features of the originally disclosed particular embodiment including surfactants with the definition of minimum and maximum pH values, specific surfactants and amounts of surfactants. These features had been individually disclosed in paragraphs [0194], [0102], [0168] and [0170] of the application as filed, but not in combination as defined in claim 1 as granted.

Claim 1 as granted therefore comprised subject-matter extending beyond the content of the application as originally filed.

(b) Claim 1 of auxiliary request 1, which defined the concentration range for the surfactant more narrowly, did not comply with Article 123(2) EPC, because it resulted in the same manner as claim 1 of the main request from selections of isolated aspects from non-convergent and non-equivalent alternatives in the original disclosure.

(c) Auxiliary request 2 was not admitted, because it was filed at a late stage and did *prima facie* not comply with Article 84 EPC.

(d) Auxiliary requests 3-7 did not comply with Article 123(2) EPC, because claim 1 of each of these requests included the same unallowable selection of features as claim 1 of the main request.

Claim 1 in each of auxiliary requests 3, 5 and 7 additionally defined a molar ratio for components of the compositions which had originally not been disclosed in the defined context.

Claim 1 in each of auxiliary requests 4 and 5 defined the composition as isotonic with body fluids. Claim 1 in each of auxiliary requests 6 and 7 defined the compositions as having an osmolality of 260-320 mOsm/kg. These features had originally not been disclosed in the defined context. Moreover, these features lacked clarity.

IV. The appellant (patent proprietor) requested with the notice of appeal of 26 May 2021 acceleration of the appeal proceedings. The Board informed the parties in its communication of 10 June 2021 that this request was granted.

V. With the statement setting out the grounds of appeal the appellant upheld the request relating to the patent as granted and filed auxiliary request 1-5.

Claim 1 of auxiliary request 1 differs from claim 1 as granted in that it defines under (d):

"0.05 mg/mL to 1.5 mg/mL surfactant selected from Polysorbate 20 and Polysorbate 80"

Claim 1 of auxiliary request 2 defines:

"An aqueous pharmaceutical composition consisting of:
(a) 50 mg/ml adalimumab;
(b) histidine buffering agent (or histidine buffer system);
(c) sugar stabiliser is selected from the group including trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol;
(d) 0.05 mg/mL to 1.5 mg/mL surfactant selected from Polysorbate 20 and Polysorbate 80;
(e) tonicifier; and
(f) water for injection
wherein the composition:
• has a pH between 5.0 and 6.7;
• is free of amino acids other than histidine; and
• free of phosphate buffering agents."

Claim 1 of auxiliary request 3 defines with respect to auxiliary request 2 additionally the feature:

"and wherein adalimumab, histidine buffering agent (or buffer system), sugar stabiliser, and tonicifier are present in a molar ratio of 1 : 14-40 : 288-865 : 28-576 respectively."

Claim 1 of auxiliary request 4 omits with respect to auxiliary request 2 the definition of the specific amount of adalimumab (50mg/ml) and defines with respect to auxiliary request 2 additionally the feature:

"said composition having an osmolality of 260-320mOsm/kg."

Claim 1 of auxiliary request 5 defines with respect to auxiliary request 3 additionally the feature:

"said composition having an osmolality of 260-320mOsm/kg".

VI. In the communication pursuant to Article 15(1) RPBA of 23 February 2022 the Board expressed *inter alia* its preliminary opinion that the main request and auxiliary requests 1-5 related to subject-matter extending beyond the content of the application as filed.

At the parties' requests the oral proceedings were held on 9 June 2022 in the form of a video conference.

VII. The arguments of the appellant relevant to the present decision can be summerized as follows:

Paragraphs [0011] to [0018] and [0032] in the section "Summary of the Invention" and paragraphs [0194] to [0213] in the section "Particular embodiments" disclosed the overarching concept of a combination of adalimumab together with a histidine buffer and a sugar stabilizer, which may additionally comprise optional components such as surfactants and tonicifiers. In line with the principles as set out in T 524/17 the skilled person would understand that the disclosure of specific aspects regarding the buffers (paragraphs [0096]-[0107]), the sugar stabilizer (paragraphs [0108]-[0121]), the tonicifiers (paragraphs [0153]-[0162]) and the surfactants (paragraphs [0163]-[0172]) may be combined with the subsequently described "Particular embodiment" of paragraph [0194], which specifically relates to a composition comprising adalumumab, a histidine buffer, a sugar stabilizer and a surfactant.

The skilled person would thus appreciate that the pH values disclosed in paragraph [0102], which extend from greater than or equal to 5.0 to less than or equal to

6.7, as well as the group of suitable sugar stabilizers disclosed in paragraph [0111], from which mannitol was merely deleted, were applicable to the embodiment of paragraph [0194]. The skilled person would on the same basis consider the disclosure of the embodiment involving Polysorbate 20 or Polysorbate 80 as surfactant in paragraph [0168] in the amounts for such surfactants defined in paragraph [0170] applicable to the embodiment of paragraph [0194]. The definition of the surfactants was further supported by the application as filed in paragraphs [0138] to [0147], which highlighted the surfactants Polysorbate 80 and Polysorbate 20 in the context of a total surfactant content of at most 1 mM. Moreover, paragraph [0170] of the application as filed specifically highlighted the concentration range for the surfactants as defined in claim 1 of auxiliary request 1.

The list of components in the particular embodiment of paragraph [0194] further represented a clear pointer towards the claimed composition comprising no or low concentrations of amino acids other than histidine as described in paragraphs [0131] to [0137] and no or low concentrations of phosphate as described paragraphs [0148] to [0152] of the application as filed.

The corresponding features in the claims of auxiliary requests 2-5 relied on the same basis in the application as originally filed.

VIII. The arguments of the respondents relevant to the present decision can be summerized as follows:

The embodiment of paragraph [0194] relating to a composition comprising a surfactant did not represent a preferred embodiment and therefore implied a first

selection with respect to the content of the application as filed. The definition of the pH range, the type and amount of surfactant, the type of sugar stabilizer as well as the defined absence or low concentration of phosphates and amino acids other then histidine involved further selections from non-convergent lists of features described in the application as filed. The combination of these selected features with the embodiment of paragraph [0194] could not be directly and unambiguously derived from the application as filed.

In addition, following the considerations concerning the disclosure of lower and upper limits in T 1919/11 the suitable pH values of 5.0 or higher, 6.3 or higher and 6.7 or lower as described in paragraph [0102] of the application as filed did not amount to disclosure of the specific range of 5.0 to 6.7, let alone the disclosure of this range specifically in relation to the histidine buffer as defined in the claims.

Furthermore, in paragraph [0168] the application as filed did not describe Polysorbate 80 and Polysorbate 20 as a preferred group of surfactants. Moreover, paragraphs [0169] and [0170] of the application as filed did not disclose the ranges for the surfactant concentration as defined in claim 1 of the patent as granted or claim 1 of auxiliary request 1 as preferred. The combined selection of these surfactants and their amounts as defined in the claims had thus also not been specifically disclosed in the application as filed.

IX. The appellant requested that the decision under appeal be set aside and the patent be maintained as granted, or that the patent be maintained on the basis of one of

auxiliary requests 1-5 submitted with the statement setting out the grounds of appeal.

In this context the appellant also requested that the case be remitted to the opposition division for consideration of the grounds for opposition raised under Articles 100(a) and 100(b) EPC.

X. Respondent 1 and respondent 2 requested in their joint reply that the appeal be dismissed.

Reasons for the Decision

Main request (patent as granted)

1. Subject-matter extending beyond the content of the application as originally filed

1.1 Basis cited by the appellant

The appellant cited paragraph [0194] of the application as originally filed as the principle basis for claim 1 as granted.

Paragraph [0194] of the application as filed presents the following disclosure:

"In an embodiment, the liquid pharmaceutical composition comprises:
- adalimumab;
- an histidine buffering agent (e.g. histidine) (or histidine buffer system);
- a sugar stabiliser (e.g. trehalose); and
- a surfactant (e.g. polysorbate 80)."

Claim 1 as granted specifies with respect to this embodiment additionally:

(a) the selected surfactants and their defined amounts: 0.05 mg/mL to 2 mg/mL of Polysorbate 20 or Polysorbate 80

(b) the pH range: between 5.0 and 6.7

(c) the list of sugar stabilizers: trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol

(d) the restrictions regarding other amino acids and phosphate buffers.

The appellant relied for the definition of these features specifically on the following passages in the application as filed, which precede the mentioned paragraph [0194]:

- paragraph [0102]: "Suitably, the liquid pharmaceutical composition has a pH greater than or equal to 5.0. Suitably, the liquid pharmaceutical composition has a pH greater than or equal to 6.3. Suitably, the liquid pharmaceutical composition has a pH less than or equal to 6.7."

- paragraph [0111]: "The sugar stabiliser is suitably selected from the group including trehalose, mannitol, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol."

- paragraph [0168]: "In a particular embodiment, the surfactant is polysorbate 80 or polysorbate 20."

and

paragraph [0170]: "Suitably, the liquid pharmaceutical composition comprises the surfactant(s) (most suitably polysorbate 80) at a concentration of from about 0.001 mg/mL to about 5 mg/mL, more suitably from about 0.01 mg/mL to about 2 mg/mL, more suitably from about 0.05 mg/mL to about 1.5 mg/mL. In an embodiment, the surfactant(s) is present at a concentration of between 0.9 mg/mL and 1.1 mg/mL, most suitably about 1.0 mg/mL. In a particular embodiment, polysorbate 80 is present at a concentration of about 1.0 mg/mL."

- paragraphs [0131] and [0148], which describe the absence or low concentrations of amino acids other than histidine and the absence or low concentrations of phosphates.

1.2 Context of the cited passages in the original disclosure

In accordance with established jurisprudence the content of the original disclosure has to be considered as a whole in the assessment of whether the combination of the features as defined in claim 1 as granted may be directly and unambiguously derived from the application as filed.

The application as originally filed discusses under the heading "Background" (see paragraphs [0002] to [0010]) the problem of long term stability of commercially available adalimumab formulations and the desirability

of alternative, less complex formulations (see paragraphs [0007] and [0010]).

Under the heading "Summary of the invention" (see paragraphs [0011] to [0034] the application as filed describes the intended invention in terms of a variety of aspects. According to the first presented aspect the invention relates to a liquid pharmaceutical composition comprising adalimumab (suitably including any biosimilar thereof), a histidine buffering agent (or histidine buffer system) and a sugar stabiliser, wherein one or more further defined components are optionally comprised or excluded (see paragraph [0011]). As explained in paragraph [0031] the composition may instead of adalimumab comprise any TNF-alpha-inhibiting antibody.

The passages specifically relied upon by the appellant are presented under the heading "Detailed description of the invention" in the section "Liquid Pharmaceutical Composition" (see paragraphs [0090] to [0214]).

This section comprises an introduction in which the invention is presented as relating to a liquid pharmaceutical composition suitably comprising a human monoclonal antibody, a histidine buffer and a sugar stabilizer, which suitably has a pH of 6.30 or higher (see paragraph [0090]). The following sub-sections describe in the first place a variety of general aspects of the liquid pharmaceutical composition, including the buffering agent or system and the pH (see paragraphs [0096] to [0107]), the sugar stabiliser (see paragraphs [0108] to [0121]), absent or low level components, including amino acids, surfactants and phosphate (see paragraphs [0122] to [0152]) and optional additional components, in particular tonifiers

and surfactants (see paragraphs [0153] to [0172]). The sub-section with the heading "Particular embodiments" (see paragraphs [0194] to [0214]) subsequently presents various more or less generic embodiments, including the generic embodiment relating to compositions comprising adalimumab, a histidine buffering agent or histidine buffering system, a sugar stabilizer and a surfactant (see paragraph [0194]).

1.3 The embodiment including surfactants

Paragraph [0172] explains in the context of surfactants as optional components that in preferred embodiments the liquid pharmaceutical composition is actually substantially or entirely free of any surfactants. The embodiment of paragraph [0194] relating to a surfactant comprising composition does therefore not represent a particularly preferred embodiment amongst the various embodiments disclosed in the sub-section "Particular embodiments".

The appellant relied on the considerations in T 524/17, in particular section 1.2, to argue that the particular embodiment described in paragraph [0194] relates to a general teaching referring to preferred features of the invention, which can therefore be combined with the disclosed more specific features regarding the sugar, the surfactant and the pH without departing from the content of the original disclosure. Taking account of the mentioned statement in paragraph [0172], which explicitly states that compositions comprising surfactants are not preferred, the Board does not find this argument persuasive.

1.4 Combination with the pH range

In the subsection "Buffer, Buffering Agent, and pH" (see paragraphs [0096] to [0107]) the liquid pharmaceutical composition is disclosed to suitably comprise a buffering agent. This buffering agent is described as most suitably an histidine buffering system (see for instance paragraph [0100]). From the expressed preference it is evident that this section of the disclosure is not restricted to histidine buffering systems. In this context the Board further notes that paragraph [0096] refers to the liquid pharmaceutical composition as a buffered solution without limitation to a histidine buffering agent and that also paragraph [0205] refers to "the buffering agent (e.g. histidine)". Moreover, the original disclosure specifically states in paragraph [0103] that especially where the buffering agent is an histidine buffering agent, the liquid pharmaceutical composition has a pH between 6.0 and 6.6. The Board therefore considers the appellant's argument, that the application as filed is only concerned with histidine buffered compositions, not convincing.

Paragraph [0102] discloses that the pH of the buffered composition is suitably 5.0 or higher, suitably 6.3 or higher and suitably 6.7 or lower. The Board is not convinced that the considerations in T 1919/11 (see section 2.2.2), in which the separate disclosure of an upper and lower limit for the concentration of an optional component of a composition was not regarded as an adequate basis for the definition of a concentration range combining the upper and lower limit, are equally applicable to the disclosure of a suitable lower and upper limit for the pH of buffered pharmaceutical compositions. However, the disclosure of the suitable upper and lower values for the pH in paragraph [0102] implies a multitude of possible ranges for the pH,

including the ranges from 5 upwards, from 6.3 upwards, from 6.7 downwards, from 5 to 6.7 and from 6.3 to 6.7. The definition of the pH range of 5.0 to 6.7 in granted claim 1 therefore still represents a further aspect of selection within the generic teaching regarding the pH in the application as originally filed.

As this range has been presented in the context of buffers in general and has not been specifically associated with an histidine buffer or buffer system, no pointer or preference links the embodiment of paragraph [0194] with the selected pH range of 5.0 to 6.7 of paragraph [0102].

The Board therefore concludes that the combination of the features of the embodiment including surfactants from paragraph [0194] with the defined pH range cannot be directly and unambiguously be derived from the application as originally filed.

1.5 Limitation to the defined surfactants in the defined concentration

In the sub-section "Optional additional components", (see paragraphs [0163] to [0172] under "Surfactant") the liquid pharmaceutical composition is disclosed to suitably comprise surfactants, most suitably a Polysorbate (polyoxyethylene glycol sorbitan alkyl esters) or Span (sorbitan alkyl esters) surfactant (see paragraphs [0164] to [0166]). In this context various particular embodiments are presented without indication of further preference, including the embodiment in which the surfactant is Polysorbate 80 or Polysorbate 20 (see paragraph [0168]).

Subsequently, the application as filed discloses suitable concentrations of surfactant, including a suitable concentration from about 0.001 mg/mL to about 5 mg/mL, more suitably from about 0.01 mg/mL to about 2 mg/mL, more suitably from about 0.05 mg/mL to about 1.5 mg/mL.

However, the Board cannot identify in the application as originally filed a preference or pointer linking the specific concentration range of 0.05-2 mg/mL with the definition of the surfactant as selected from Polysorbate 80 or Polysorbate 20.

The appellant's argument that the application as filed highlights Polysorbate 80 and Polysorbate 20 by only specifically mentioning these surfactants in the context of surfactants that may be present in a concentration up to 1mM (see paragraphs [0138] and [0145]) is not considered convincing. This part of the disclosure presents under the heading "Low/No Surfactants" specific aspects of compositions in which surfactants are absent or only present in low concentrations. The mention of specific surfactants in this particular context cannot be considered as basis for any preference of these surfactants in compositions characterized by the presence of surfactant as described in paragraph [0194].

The Board therefore concludes that the limitation of the embodiment involving surfactants from paragraph [0194] by including the combination of features regarding the specific concentration with the specific surfactants as defined in claim 1 as granted can also not be directly and unambiguously derived from the application as originally filed.

1.6 Accordingly, the Board confirms the conclusion in the decision under appeal that the patent as granted includes subject-matter extending beyond the application as originally filed.

Auxiliary requests 1-5

2. Auxiliary request 1

2.1 Claim 1 of auxiliary request 1 corresponds to claim 1 as granted except for the definition of the concentration of the surfactant, which is defined to range from 0.05-1.5 mg/mL.

2.2 The Board observes that claim 1 of auxiliary request thus includes the same combination of the features of the embodiment involving surfactants from paragraph [0194] with the defined pH range as claim 1 of the main request. The same considerations as set out in section 1.4 with respect to the main request therefore equally apply with respect to claim 1 of auxiliary request 1.

2.3 The Board further acknowledges that the concentration range of 0.05-1.5 mg/mL is described as "more suitable" in paragraph [0170] of the application as filed.

However, the original disclosure provides in paragraph [0169] also alternative definitions of suitable and more suitable surfactant concentrations expressed in mM:

"Suitably, the liquid pharmaceutical composition comprises the surfactant(s) (most suitably polysorbate 80) at a concentration of from about 0.0001 to about 5 mM (i.e. 0.1 µM-5mM), more suitably from about 0.001 to about 2 mM, more suitably from about 0.01 to about 1.0

mM. In an embodiment, the surfactant(s) is present at a concentration of between 0.72 and 0.80 mM, most suitably about 0.76 mM. In an embodiment, polysorbate 80 is present at a concentration of 0.76 mM."

Taking account of the molecular weight of the preferred surfactant Polysorbate 80 (approximately 1300 g/mol) the alternative definitions of suitable and more suitable surfactant concentrations presented in paragraph [0169] in terms of mM do not correspond to the definitions presented in paragraph [0170] in terms mg/mL. In view of this evident multiplicity in the definition of suitable and more suitable surfactant concentrations, the Board does not recognize a clear preference in the application as filed with respect to the surfactant concentrations as defined in claim 1 of auxiliary request 1.

The Board therefore concludes that the defined specific concentration range of 0.05-1.5 mg/mL is not linked by a preference or pointer to the definition of the surfactant as selected from Polysorbate 80 or Polysorbate 20. The same considerations as set out in section 1.5 with respect to the main request therefore also apply with respect to claim 1 of auxiliary request 1.

2.4 Accordingly, the Board concludes that claim 1 of auxiliary request 1 includes subject-matter extending beyond the application as originally filed and thereby contravenes the provision of Article 123(2) EPC.

3. Auxiliary request 2-5

The independent claims of each of auxiliary requests 2-5 include with respect to paragraph [0194] of the

application as filed the same additional features as discussed in sections 1.1 and 2.1 above with respect to claim 1 as granted and claim 1 of auxiliary request 1. The appellant referred for the basis of these features in the independent claims of auxiliary requests 2-5 to the same passages of the application as filed relied upon for the main request and auxiliary request 1 and did not provide any additional argumentation. The Board therefore concludes that claim 1 in each of auxiliary requests 2-5 comprises subject-matter extending beyond the content of the application as originally filed for the same reasons as explained above in relation to main request and auxiliary request 1.

Auxiliary requests 2-5 do therefore not comply with Article 123(2) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated