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Datasheet for the decision of 20 June 2024

Case Number: T 0466/23 - 3.3.07

Application Number: 15723695.1

Publication Number: 3145488

IPC: A61K9/00

Language of the proceedings: EN

Title of invention:
LIQUID PHARMACEUTICAL COMPOSITION

Patent Proprietor:
Fresenius Kabi Deutschland GmbH

Opponents:
Biogen Inc.
Samsung Bioepis NL B.V.

Headword:
Liquid adalimumab pharmaceutical composition / FRESENIUS

Relevant legal provisions:
EPC Art. 100(c), 123(2), 100(a), 54, 56

Keyword:
Grounds for opposition - extension of subject-matter (no)
Novelty - (yes)
Inventive step - (yes)

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Beschwerdekammern

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Case Number: T 0466/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 20 June 2024

Appellant: (Opponent 1)	Biogen Inc. 225 Binney Street Cambridge, MA 02142 (US)
Appellant: (Opponent 3)	Samsung Bioepis NL B.V. Olof Palmestraat 10 2616 LR Delft (NL)
Representative:	Patent Boutique LLP 10A Printing House Yard Hackney Road London E2 7PR (GB)
Respondent: (Patent Proprietor)	Fresenius Kabi Deutschland GmbH Else-Kröner-Strasse 1 61352 Bad Homburg v.d.H. (DE)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 December 2022 rejecting the opposition filed against European patent No. 3145488 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	S. Ruhwinkel

Summary of Facts and Submissions

I. European patent 3 145 488 (hereinafter "the patent") was granted on the basis of one single claim, which read as follows:

"1. A liquid pharmaceutical composition consisting of:

- 50 mg/ mL adalimumab;
- a citrate buffering system;
- a sugar stabiliser;
- a tonicifier;
- a surfactant; and
- water (for injection);
- wherein said adalimumab, citrate buffer system, sugar stabiliser, tonicifier, and surfactant are present in a molar ratio of 1 : 14-40 : 288-865 : 28-576 : 0.1-3.2 respectively."

II. Three oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step (Article 100(a) EPC), it was not sufficiently disclosed (Article 100(b) EPC) and it extended beyond the content of the application as originally filed (Article 100(c) EPC).

III. During the first instance proceedings opponent 2 withdrew its opposition and was consequently since then no longer party to the proceedings.

IV. The opposition division took the decision to reject the oppositions.

V. The decision of the opposition division, posted on 22 December 2022, cited *inter alia* the following documents:

D1: A. Bender, Prior Art Publishing, Publication No. PAPDEOTT002384, 6 February 2013
D2: Indian Patent Application No. 1606/MUM/2012 filed 30 May 2012 (as priority document for WO 2013/164837) which became available to the public on publication of WO 2013/164837 (7 November 2013)
D3: WO 2014/039903 A2
D4: Humira® Label
D5: Meaning of "stipulate" in the Cambridge English Dictionary
D8: Warne, Chapter 6 "Formulation Development of Phase 1-2 Biopharmaceuticals: An Efficient And Timely Approach" in Formulation and Process Development Strategies for Manufacturing Biopharmaceuticals, ed. Jameel and Hershenson, John Wiley & Sons, Inc. (2010)
D18: WO 2013/164837 A1
D20: Declaration of Professor Sven Frøkjær, 2022

VI. The opposition division came to the conclusions that the subject-matter of granted claim 1 fulfilled the requirements of Article 123(2) EPC and the patent as granted met the requirements of Articles 83, 54 and 56 EPC.

VII. The opponents 1 and 3 (hereinafter the appellants) lodged an appeal against the above decision of the opposition division.

VIII. With its reply to the appellants' statement setting out the grounds of appeal the patent proprietor (hereinafter the respondent) defended its case on the basis of the patent as granted as the main request, and

on the basis of auxiliary requests 1 to 19 filed therewith.

IX. Oral proceedings were held before the Board on 20 June 2024.

X. The appellants requested that the decision under appeal be set aside and that the patent be revoked. They further requested that auxiliary requests 1 to 19 filed during the first instance proceedings on 26 August 2022 and resubmitted with the reply to the statements of grounds of appeal not be admitted into the appeal proceedings.

XI. The respondent requested that the appeals be dismissed, *i.e.* that the patent be maintained as granted (main request), or that the patent be maintained on the basis of one of the auxiliary requests 1 to 19 filed during first instance proceedings on 26 August 2022 and resubmitted with the reply to the statements of grounds of appeal.

XII. The arguments of the appellants, as far as relevant for the present decision, can be summarised as follows:

(a) The subject-matter of claim 1 of the main request did not meet the requirements of Article 123(2) EPC. The combination of features of granted claim 1 would be the result of selections from multiple lists without any pointer thereto. The embodiment defining the claimed molar ratio, the concentration of adalimumab and the limitation of the claimed composition by the terms "consisting of" each required a selection. Furthermore the definition in the original application of the composition with the term "consisting of" was limited to

compositions defined in terms of specific ingredients not in terms of classes of components as in claim 1 of the main request.

(b) The main request did not meet the requirements of Article 54 EPC.

The composition disclosed on page 4 of D1 when the buffer was buffer 4), option 4b) as defined in table 1 of D1 anticipated the subject-matter of claim 1. In particular, the adalimumab concentration of 50 mg/ml would be implicitly the preferred one and the remaining ranges of excipients amounts overlapped to a significant extent with those defined by the presently claimed molar ratios.

The implicitly disclosed compositions "CE1-3", corresponding to compositions of examples 1-3 of D2 wherein the phosphate buffer was replaced by a citrate buffer as disclosed in the paragraph below the table of examples 1-30, anticipated the subject-matter of claim 1. Moreover, the molar ratios corresponding to the ranges of amounts disclosed for examples 1 to 3 overlapped with the claimed molar ratios.

(c) The subject-matter of claim 1 of the main request did not involve an inventive step starting from D3 but also from D18, D2, D1 or D4, which all represented suitable starting points.

Starting from D3 as closest prior art, formulation 3 of Table D constituted the closest embodiment. The claimed formulation differed therefrom in that it contained a lower concentration of citrate

buffer and a higher amount of mannitol. In the absence of any technical effect, the objective technical problem resided in the provision of an alternative adalimumab composition. The claimed concentrations would represent arbitrary features, which were encompassed by the concentration ranges generally disclosed in D3 for the buffers and for mannitol. D3 did not provide any indication that citrate could not be used. Citrate was actually disclosed as acceptable in all embodiments, even if not preferred. No pointer was required in the present case merely aiming at the provision of an alternative formulation without any particular effect. In any case, D3 disclosed formulations with a lower concentration of citrate as well as a concentration of mannitol of more than 150 mM, preferably 200 mM, when used as stabiliser. Accordingly, the claimed subject-matter was not inventive over D3.

D18 disclosed formulations overlapping with the formulation of claim 1 of the main request (see embodiment on page 3 lines 26-32, and more specific features on pages 6 to 8). During oral proceedings, the presently claimed formulation was considered to differ from the specific examples of D18 at least in the nature of the buffer used and the specific molar ratio of the components. In the absence of any technical effect, the objective technical problem resided in the provision of an alternative adalimumab composition being more concrete than the one generally defined on page 3. The selection of the citrate buffer and of concentrations corresponding to the presently claimed molar ratios constituted an arbitrary selection of equally disclosed alternatives in D18 which did not require

any incentive. As a result the claimed subject-matter was obvious starting from D18.

Starting from D2 as closest prior art, the formulation of example 73 was considered during oral proceedings to represent the closest embodiment. The claimed formulation differed from this formulation of D2 in the nature and concentration of the buffer, hence the molar ratios between components. The objective technical problem resided in the provision of an alternative adalimumab composition. A similar reasoning as starting from D18 applied, since D2 generally disclosed citrate buffer as well as a preferred concentration range thereof overlapping with the present definition of molar ratios. As a result the claimed subject-matter was obvious starting from D2.

D1 provided a concrete disclosure of a composition corresponding to Humira® with 10 mM citric acid as buffer. During oral proceedings the distinguishing feature was identified as being a higher amount of mannitol in compositions according to claim 1 of the main request. The objective technical problem resided in the provision of an alternative adalimumab composition. A similar reasoning as starting from D18 applied, since D1 generally disclosed a range of 2 to 25 mg/ml of mannitol (see page 5 of D1) and the value of 25 mg/ml would lead to a molar ratio according to the present claim. As a result the claimed subject-matter was obvious starting from D1.

Furthermore, D1, D2 and D18 were to be considered on their own and not to be read or interpreted in

the light of D3. D3 being an isolated patent publication could also not establish the presence of a technical prejudice in the art against the use of citrate buffer.

The claimed formulation differed from the commercial product Humira® disclosed in D4 in the amount of mannitol (higher in claim 1) and the nature of the buffer (only citrate in claim 1). The objective technical problem resided in the provision of an alternative adalimumab composition. It would have been obvious to remove the phosphate buffer in view of the drawbacks described for this buffer in D8 and to increase the amount of mannitol to compensate for the impact of the loss of phosphate buffer on the tonicity of the formulation. As a result the claimed subject-matter was not inventive starting from D4.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) Claim 1 of the main request found basis in the original application. The embodiment described in paragraph [0189] did not require any selection, the concentration of adalimumab was directly and unambiguously derivable as the preferred concentration and the term "consisting of" as disclosed in original paragraph [0081] applied to all the "particular embodiments" of the description. Finally there was no clear distinction in the application between ingredients and components. The requirements of Article 123(2) EPC were thus fulfilled.

(b) The main request met the requirements of Article 54 EPC.

D1 did not provide any direct and unambiguous disclosure of a specific composition of adalimumab, in particular one containing 50 mg/ml adalimumab and concentrations of the mandatory components corresponding to the presently claimed molar ratios.

The examples of compositions described in D2 did either not contain a citrate buffer or contained different excipients than the ones of claim 1 of the main request. Moreover the paragraph below the table of examples 1-30 did not support an implicit disclosure of the fictitious compositions "CE1-3".

(c) The main request met the requirements of Article 56 EPC.

D3 represented the closest prior art document and the closest embodiment therein was to be found in Table M describing optimum formulations. However, even starting from formulation 3 of Table D, the claimed subject-matter involved an inventive step. The distinguishing feature between this prior art formulation and the claimed one resided in the concentration of the citrate buffer (lower in the claimed composition) and the one of mannitol (higher in the claimed composition). The objective technical problem resided in the provision of an alternative liquid pharmaceutical adalimumab formulation. In this context alternative was to be understood as a viable formulation with respect to the commercial product Humira®. Overall D3 provided the clear teaching to increase the citrate buffer

concentration to maintain stability of the composition compared to Humira®, so that the skilled person willing to solve the problem posed would not have reduced this concentration. Furthermore, there was no teaching in D3 to increase the concentration of mannitol to compensate for any potential stability issue with the citrate buffer. The claimed subject-matter was therefore inventive over D3.

D18, D2, D1 and D4 were not appropriate choices as closest prior art. However the claimed subject-matter was also inventive over these documents.

The claimed formulation differed from the specific examples of D18 in the specific molar ratios of the excipients, a simpler system and the use of sugar stabilisers. The objective technical problem resided in the provision of a simplified, viable adalimumab composition. D18 did not provide any pointer to the modifications leading to the present solution.

Starting from D2 as closest prior art, the closest embodiment should be one of the formulations comprising a citrate buffer. However, starting from the formulation of example 73, the claimed formulation differed therefrom in the nature and concentration of the buffer. The skilled person willing to modify the buffer for citrate buffer would have considered the citrate based formulations disclosed in the examples of D2. They were however more complex and contained further stabilisers. Moreover, the skilled person having knowledge of D3 would actually be discouraged from using citrate buffer at a low concentration. Hence,

D2 did not provide any indication towards the present solution.

D1 did not disclose any specific formulation. The objective technical problem resided in the provision of a specific viable pharmaceutical adalimumab composition. D1 itself stated that the nature and the concentration of the buffer might have an impact on the stability of the formulated antibody. D1 did therefore not provide any indication that using the listed citrate buffer at the disclosed concentration would provide a viable pharmaceutical adalimumab composition. The skilled person having knowledge of D3 would furthermore be discouraged from using citrate buffer at a low concentration.

Starting from the commercial product Humira® disclosed in D4, the objective technical problem resided in the provision of an alternative pharmaceutical adalimumab formulation being simpler in composition. It would not have been obvious to remove the phosphate buffer from D4 alone. The drawbacks of the phosphate buffer mentioned in D8 were observed in the context of freezing of the formulation. The skilled person would thus merely have avoided freezing the formulation of D4, in line with the recommendation of D4 to store the liquid formulation at 2 to 8 °C. Even if the skilled person would have removed the phosphate buffer, the prior art provided no motivation to increase the amount of mannitol as a compensation.

Reasons for the Decision

Main request - Granted patent

1. Amendments

1.1 It was uncontested that granted claim 1 is based on the embodiment disclosed in the last sentence of original paragraph [0189], wherein:

(a) the concentration of adalimumab was added based on the last sentence of original paragraph [0090],

(b) the term "comprising" was replaced by "consisting of" as generally described in original paragraphs [0081] and [0082], and

(c) water was added as diluent based on the last sentence of original paragraph [0116].

1.2 The appellants however contested that the combination of features of granted claim 1 would be directly and unambiguously derivable from the original application, since it would be based on selections from multiple lists (last sentence of paragraph [0189] and features (a) and (b) above) without any pointer thereto.

1.3 The appellants argued that it would be required to select first the original paragraph [0189] and then the last sentence thereof. The Board considers that the last sentence of original paragraph [0189] represents an individual embodiment described among several other equally described alternative embodiments under the heading "Particular Embodiments". The selection of this self contained alternative embodiment therefore represents at most a one-fold selection out of all the equally disclosed alternative embodiments.

Furthermore, as explained by the respondent, the subject-matter of claim 1 does not appear to be based on the combination of 4 individual unrelated features but on an individual embodiment combining the components of the claim (last sentence of paragraph [0189]) to which further characterisations have been added (modifications (a) to (c)). Contrary to the opinion of the appellants, a pointer to the selection of the embodiment of the last sentence of original paragraph [0189] is consequently not required.

1.4 The appellants further explained that the claimed concentration of adalimumab would require a further selection within original paragraph [0090] without this specific concentration being particularly preferred and without any pointer thereto. The Board agrees with the impugned decision and the respondent that the skilled person would understand the specific concentration of 50 mg/ml as representing the preferred concentration due to the unambiguous convergent formulation of the paragraph. Despite the absence of explicit preference ("in an embodiment" used throughout the paragraph), the ranges listed in this paragraph converge around the value of 50 mg/ml individually disclosed in the final sentence of the paragraph. Moreover this concentration has been used in all the examples, which provides a further indication of its implicit preference.

In this context the appellants further argued in writing that there would be a teaching away to combine the adalimumab concentration with molar ratios, which are defined in the embodiment of the last sentence of original paragraph [0189]. This argument of the appellants was based on a passage of original paragraph [0081] stating that "the relative ratios between components is often more important than the absolute

concentration thereof". However it appears from the sentence following the one cited by the appellants in original paragraph [0081] that it is merely "not necessary" to specify absolute concentrations of ingredients. In the Board's view, this does not mean that features defining molar ratios cannot be combined with a feature defining the absolute concentration of the active ingredient.

During oral proceedings, the appellants disputed this understanding of the Board and considered that the lack of necessity could not be understood as a teaching that the defined molar ratios could be combined with an absolute concentration of the active ingredient. According to the appellants, the teaching of this paragraph remained that the concentration was not important. In the appellants' view, this was even more the case as there was no preferred concentration of adalimumab disclosed in the original application. This argument is not convincing. For the reasons detailed above, the Board is satisfied that the concentration of 50 mg/ml for adalimumab is directly and unambiguously derivable from the application as being the preferred one. Hence, the Board considers that the adalimumab concentration disclosed in original paragraph [0090] would be understood as applying to any composition disclosed in the original application, *i.e.* including the one defined in the last sentence of paragraph [0189].

During oral proceedings the respondent further indicated that original paragraph [0056] provided a link between the 50 mg/ml adalimumab concentration and the calculation of the molar ratios according to the invention. Contrary to the opinion of the appellants, this passage does not relate to Humira® and confirms

that the claimed molar ratios can be combined with a specific concentration of adalimumab, in particular the one of 50 mg/ml, when defining the invention.

It follows that the combination of the concentration of adalimumab disclosed in the last sentence of original paragraph [0090] with the embodiment disclosed in the last sentence of original paragraph [0189] is directly and unambiguously derivable from the original application in accordance with the Gold standard.

1.5 Contrary to the appellants' opinion, the Board considers that the teaching provided in original paragraphs [0081] and [0082] regarding compositions defined as consisting of the listed ingredients applies to any of the compositions disclosed in the section "Particular Embodiments" *i.e.* also to the embodiment defined in the last sentence of original paragraph [0189].

The argument of the appellants concerning the interpretation of the expression "stipulated ingredients" as necessarily referring to specific ingredients and not to functionally defined ones is not convincing. An overly literal approach should indeed be avoided. Furthermore the definition of the term "stipulate" as provided in D5 does not exclude the stipulation by generic terms. Furthermore the appellants' argument concerning a different meaning of the terms ingredients and components is also not convincing because the original application does not provide any clear and unambiguous distinction between those two terms, which are usually used interchangeably in the art.

1.6 Accordingly, the main request fulfils the requirements of Article 123(2) EPC and the ground of opposition under Article 100(c) EPC does not prejudice the maintenance of the patent.

2. Sufficiency of disclosure

The appellants did not pursue in the appeal stage the objection under Article 100(b) EPC. The Board agrees with the impugned decision that the ground of opposition under Article 100(b) EPC does not prejudice the maintenance of the patent.

3. Novelty

3.1 Novelty over D1

3.1.1 The appellants argued that the subject-matter of claim 1 of the main request would not be novel over the composition disclosed on page 4 of D1 when the buffer is buffer 4), option 4b) as defined in table 1 of D1.

3.1.2 As argued by the respondent, D1 does not provide a direct and unambiguous disclosure of a composition comprising specifically 50 mg/ml adalimumab. Merely a range of 45-55 mg/ml is disclosed for the composition generally defined on page 4.

3.1.3 The appellants argued that, as explained in D20, the skilled person would use adalimumab at a concentration of 50 mg/ml. This argument is not convincing since the relevant question in the context of novelty is exclusively what is directly and unambiguously disclosed in a prior art document, not what the skilled person would do or not.

3.1.4 The appellants also insisted on the fact that the same requirements should be applied when assessing the disclosure of the original application in the context of Article 123(2) EPC and when assessing the disclosure of a prior art document in the context of Article 54 EPC. According to the appellants, if the concentration of 50 mg/ml would be considered as implicitly disclosed as the most preferred concentration in the original application then the same should apply to D1. Indeed the value of 50 mg/ml would be encompassed by both ranges for the composition of page 4 of D1 and would be specifically identified on pages 2 and 3 of D1.

This argument is however not convincing. The specific value of 50 mg/ml is nowhere specifically disclosed for the composition described on page 4 of D1. This concentration is referred to in D1 exclusively in the context of the commercial product Humira®. In contrast the value of 50 mg/ml is explicitly singled out for the compositions of the invention in the original application underlying the patent. Both disclosures (original application and D1) are therefore different in this respect.

3.1.5 Furthermore, the appellants brought forward that the molar ratios corresponding to the ranges of amounts disclosed on page 4 would overlap with the claimed ones. However, the mere overlap of concentration ranges of individual components is not sufficient to anticipate the claimed molar ratios, let alone in combination with the specific concentration of adalimumab claimed.

3.2 Novelty over D2

3.2.1 The appellants argued that the subject-matter of claim 1 of the main request would not be novel over the implicitly disclosed compositions "CE1-3", corresponding to the compositions of examples 1-3 of D2 wherein the phosphate buffer would have been replaced by a citrate buffer as disclosed in the paragraph below the table of examples 1-30.

3.2.2 The parties disagreed on the interpretation of the paragraph below the table of examples 1-30 and above the table of examples 31-84.

3.2.3 The Board observes that it is ambiguous whether this paragraph is actually meant:
(a) to apply to the compositions of examples 1-30 (as argued by the appellants), or
(b) as an introduction to examples 31-84 (as argued by the respondent).
There is indeed no explicit reference to any of the previous or following compositions in said paragraph.

3.2.4 Furthermore also the wording of the paragraph itself is ambiguous. The parties disagreed on the type of buffers actually mentioned in this paragraph. The appellants considered that the expression "with Arginine and the like" would refer only to the last buffer recited based on a literal interpretation and on the fact that the compositions in the preceding table did not include any arginine. On the other hand, the respondent appeared to follow the opinion of the opposition division which considered that it would apply to all the buffers cited in the paragraph, *i.e.* including citrate. This interpretation was based on the fact that several compositions in the following tables indeed contain the

listed buffers (including citrate) only together with arginine. However the Board notes that this following table recites also compositions with buffers not cited in the intermediate paragraph.

3.2.5 It follows that it cannot be unambiguously determined: (i) which buffers are really meant in the paragraph in question (with or without addition of arginine), and (ii) whether the paragraph in question refers to
- formulations to be built from those of examples 1-30 by replacement of the buffer, or
- some of the formulations listed in the following table.

There is therefore no clear and unambiguous disclosure of a formulation comprising adalimumab and a citrate buffer in the absence of any arginine.

3.2.6 Furthermore in the paragraph in question no concentration is given for the citrate buffer, so that it also fails to disclose amounts which may correspond to the claimed molar ratios. Contrary to the opinion of the appellants, there is no indication in D2 that the citrate buffer would be used at the same concentration and pH as the disclosed phosphate buffer of examples 1 to 3.

3.2.7 Moreover, the appellants brought forward that the molar ratios corresponding to the ranges of amounts disclosed for examples 1 to 3 would overlap with the claimed ones. Notwithstanding the above issues of the actual disclosure of adalimumab formulations having only citrate as buffer, the Board notes that the mere overlap of concentration ranges of individual components would not be sufficient to anticipate the claimed molar ratios.

3.2.8 Accordingly, D2 does not directly and unambiguously disclose adalimumab compositions in a citrate buffer without arginine and with molar ratios for the various excipients according to present claim 1.

3.3 Novelty over D18

The appellants did not pursue in the appeal stage the objection of lack of novelty over D18. The Board agrees with the impugned decision that the subject-matter of the main request is novel over D18.

3.4 Conclusion on novelty

Accordingly, the subject-matter of the main request is novel over the cited prior art documents and the ground of opposition under Article 100(a) EPC in combination with Article 54 EPC does not prejudice the maintenance of the patent.

4. Inventive step

4.1 Closest prior art

4.1.1 The patent relates to adalimumab formulations. The purpose as stated in the description is the provision of an alternative formulation having comparable or improved performance compared to the commercial product Humira® but containing fewer components (see *e.g.* paragraph [0007]).

4.1.2 The parties disagreed on the choice of the closest prior art. The appellants argued that D3 but also D1, D2, D4 and D18 would each represent suitable starting points for the assessment of inventive step. The

respondent, in line with the decision of the opposition division, considered that D1, D2, D4 and D18 are not appropriate as closest prior art and that D3 should be chosen.

4.1.3 In this context, as argued by the appellants, it is established case law that the claimed subject-matter must be non-obvious having regard to any prior art(Case Law of the Boards of Appeal, 10th Edition, 2022, I.D. 3.1, page 191, 2nd full paragraph). If several documents constitute realistic starting points, then the claimed subject-matter must be inventive over all of them for an inventive step to be acknowledged.

4.1.4 In the present case, the Board agrees with the opposition division and the respondent that D3 appears closer to the specific purpose of reducing the number of components compared to Humira® since all the examples do indeed contain less excipients than the commercial composition. Furthermore this document which generally aims at the provision of stable adalimumab formulations (see title, page 1 paragraph 1, page 2 lines 21-22) provides experimental results regarding the stability of the prepared formulations.

However, as brought forward in details by the appellants, D18, D2 and D4 cannot be considered as unrealistic starting points. All three documents disclose adalimumab formulations, which are generally described as stable (see improved formulations aiming at stabilising the antibody during storage in D18, page 1; see alternative compositions aiming at reducing aggregation of the antibody in D2, page 1; see Humira® in D4). Moreover, while D2 and D18 do not explicitly mention the aim of reducing the number of excipients, both documents disclose formulations generally having

the same amount of excipients as present compositions. Hence, inventiveness also had to be assessed over D18, D2 and D4 as closest prior art documents.

As far as D1 is concerned, the Board considers this document indeed less appropriate as starting point since it does not disclose any specific adalimumab composition (merely a generally defined composition). However the appellants insisted on a different interpretation of the disclosure of D1. Hence, inventiveness starting from D1 was also discussed.

4.2 Problem - solution approach starting from D3

Starting embodiment and distinguishing feature

4.2.1 Starting from D3 as closest prior art, the parties disagreed on which embodiment of D3 to start from. The respondent agreed with the opposition division's decision to select a composition of table M since the compositions of this table would be the most preferred ones. In the respondent's view, D3 would teach away from the compositions having citrate buffer such as formulations of the Block D formulation studies. The appellants on the other hand considered the formulation 3 of Table D as the closest one since it represented an adalimumab formulation having the same number and nature of excipients as the claimed composition. In the appellants' view, the overall disclosure of D3 would not teach away from such formulation as an alternative.

4.2.2 The Board considers that, even if the compositions of table M appear indeed to be disclosed as preferred compositions in D3 in terms of stability, D3 does not teach away from the formulation 3 of Table D.

In particular, the general statement on page 2 line 29 of D3 mentioned by the respondent and specifying "and preferably does not comprise any citrate buffer" cannot be understood as an absolute teaching away from using citrate buffer *per se*. Citrate buffer is indeed listed three lines above in the same paragraph as one of the possible alternative buffers to be used in the invention. As will be detailed below (see 4.2.9 to 4.2.11), the teaching of D3 is rather that citrate buffer requires specific concentration conditions to avoid affecting the stability of the formulation.

Furthermore, as underlined by the appellants, formulation 3 of Table D is described in D3 as providing a better stability than the combination phosphate/citrate buffer used in Humira® (see page 57 lines 26-27).

In this context the Board generally agrees with the respondent that the entire content of D3 must be taken into account. However, the fact that further improved compositions using different buffer systems are described in the subsequent sections of D3 does not undermine this finding that the formulation 3 of Table D would provide at least an alternative to the commercial Humira® composition.

4.2.3 Accordingly, the Board accepts the appellant's position that formulation 3 of Table D is a suitable starting point for assessing inventive step.

4.2.4 During oral proceedings it was undisputed that the claimed formulation differed from formulation 3 of Table D of D3 in the molar ratios between the components. In particular, in the claimed compositions the amount of citrate is lower and the amount of

mannitol is higher than in formulation 3 of Table D of D3.

Technical effect and objective technical problem

4.2.5 No particular technical effect, including in terms of stability, specifically demonstrated for this difference compared to the closest prior art has been brought forward by the respondent. As underlined by the appellants, the patent provides general statements on overall effects in terms of stability and viability but without linking them to any particular feature of the claim, let alone the present distinguishing features over the closest prior art. An improvement over the closest prior art cannot therefore be acknowledged.

4.2.6 The Board therefore considers that, starting from formulation 3 of Table D of D3, the objective technical problem to be solved resides in the provision of an alternative adalimumab composition.

4.2.7 In this context the respondent insisted on the fact that, according to the patent, the claimed compositions are viable. In the absence of any specific definition of the "viability" of a pharmaceutical composition in the patent, the Board understands this criteria as implying a formulation suitable for administration to a subject, as Humira®. The patent provides experimental evidence that compositions according to the claims of the main request indeed have similar performance in terms of thermal stability as Humira® (see formulations DoE2-5 and DoE2-6, formulations 5 and 6 in table 3 and paragraph [0281] as well as the composition described in paragraph [0282] of the patent). Since D3 also aims at providing alternative compositions to Humira® with comparable or even improved stability, and in absence

of any evidence that the formulations provided in D3 would not be suitable for administration to a subject, the formulations of D3 are also to be considered as "viable" in the sense of the patent.

4.2.8 It follows that the provision of an alternative composition implicitly requires the provision of a "viable" formulation, *i.e.* a formulation having comparable stability to the formulation 3 of Table D of D3 and to Humira®. This requirement does not need to be further included in the formulation of the objective technical problem. Nevertheless, this requirement cannot be ignored when assessing the obviousness of the solution in the present case.

Obviousness of the solution

4.2.9 The teaching of D3 was extensively discussed during oral proceedings. While the Board considers that overall D3 does not teach away from adalimumab compositions with citrate buffer *per se*, the skilled person would have learned from D3 that, contrary to other buffers disclosed therein such as Histidine, citrate buffer does not constitute a "universal" buffer for the reasons detailed below.

4.2.10 On the one hand, D3 mentions citrate as one of the possible buffers according to the invention (see *e.g.* page 2 lines 25-26, page 3 lines 4, 20 and 29, page 23 line 5) but on the other hand it is not the preferred one and it is even avoided in certain embodiments (see *e.g.* page 2 line 29, page 6 lines 11-12, page 21 lines 4-12).

4.2.11 As argued by the respondent, when taking into account the experimental studies of D3, it appears clear that

citrate buffer constitutes an acceptable buffer under given conditions, namely when used at a concentration of at least 20 mM. The reasons are the following:

(a) In the Block A formulation studies the various buffers were tested at a concentration of 10 mM and the conclusion is that the citrate formulation exhibited the poorest stability, in particular poorer than the composition corresponding to the commercial Humira® product (see page 33 lines 2 to 4 and Figures 1 and 2). This poor performance of formulations with citrate buffer at 10 mM was confirmed in Block B formulation studies (see formulation 2) as well as in Block D formulation studies (see formulations 13 and 14 which were said to lead to higher impurity levels, see pages 51, 52 and 58 lines 9-10).

(b) When however used at a concentration of 20 mM or higher, the citrate buffer is reported to perform in terms of stability at at least a comparable level as the other buffers and the mixed phosphate / citrate buffer of the commercial product Humira® (see Block D formulation studies, formulations 3 and 4, tables D-2 to D-5 and Block F formulation studies, formulation 8, table F and page 67 line 9).

4.2.12 In this context the appellants argued that the skilled person would recognise that the differences obtained in the Block A formulation studies in terms of stability are not significant. Furthermore, should the skilled person have any doubt regarding the use of citrate buffer based on these results, they would recognise that these are due to the low concentration of mannitol. Indeed when increasing the concentration of

mannitol in the formulations of Block D formulation studies, then the formulations with citrate buffer would perform better than Humira®.

4.2.13 These arguments are not convincing. It remains that in the Block A formulation studies, the amount of mannitol was kept constant in all the tested formulations including the one corresponding to the commercial product Humira®, so that a true comparison of the buffers appears credible. Even if the differences in terms of purity are modest, the citrate buffered formulation is the sole formulation performing worse than Humira® in the assays of this study (see Figures 1 and 2). Finally, as stated above in the Block D formulation studies, the citrate buffered formulations performing better than Humira® contain 20 mM citrate (formulations 3 and 4) while those with 10 mM citrate are said to lead to higher amounts of impurities (formulations 13 and 14).

4.2.14 Finally regarding the general passages of the description of D3 mentioning concentrations of about 5 mM to about 50 mM for the buffer (see page 18 lines 1 to 2 and page 21 lines 28 to 29) referred to by the appellants, the Board considers that the skilled person would identify this range as the broadest possible one applying generally to the disclosed buffers. The skilled person would however further recognise, for the reasons detailed above, that citrate buffer cannot be considered as a universally applicable buffer according to D3 but requires specific conditions to maintain the performance of the formulations in terms of stability.

4.2.15 The Board is therefore of the opinion that the skilled person starting from formulation 3 of Table D, containing 20 mM citrate, would not have lowered the

concentration of citrate buffer with the aim of providing an alternative adalimumab composition, *i.e.* a composition performing equally well in terms of stability.

4.2.16 Contrary to the opinion of the appellants, the Board is further of the opinion that the skilled person would also not have increased the concentration of mannitol to compensate for a potential loss of stability due to the reduction of the concentration of citrate. While mannitol is indeed acknowledged in D3 as stabiliser if used at concentrations exceeding 150 mM (see paragraph bridging pages 107 to 108), it remains that it is not the preferred stabiliser according to D3 (see two first lines of paragraph bridging pages 107 to 108). Moreover, there is no clear suggestion in D3 that the technical problem of providing an alternative to formulation 3 of Table D could be solved by increasing the amount of mannitol in order to compensate for the loss of stability due to the reduction of the concentration of citrate. The idea that the skilled person would modify the composition of formulation 3 of Table D by decreasing the amount of citrate and increasing the amount of mannitol disregards the constraints that the skilled person would derive from the teaching of D3 in terms of modifications that do not compromise the stability of the composition.

4.2.17 As a result, the subject-matter of the main request meets the requirements of inventive step starting from D3 as the closest prior art.

4.3 Problem - solution approach starting from D18

4.3.1 D18 generally discloses a formulation overlapping with the formulation of claim 1 of the main request (as

detailed by the appellants, see embodiment page 3 lines 26-32, and more specific features on pages 6 to 8). During oral proceedings, it was undisputed that the presently claimed formulation differed from the specific examples of D18 at least in the nature of the buffer used and the specific molar ratio of the components.

4.3.2 In the absence of any particular effect directly linked to these features compared to the compositions of D18, the objective technical problem to be solved can be formulated in a similar manner as when starting from D3, namely as the provision of an alternative adalimumab composition. The same consideration regarding the "viability" and maintenance of the stability as when starting from D3 as closest prior art apply (see 4.2.8).

4.3.3 As argued by the appellants, the skilled person could in principle have modified the specific compositions of D18 within the ambit of the general disclosure of D18 so as to arrive at compositions according to the present main request. Citrate buffer is indeed mentioned in a list of possible buffers (see page 6 line 21) and the concentration of 10 mM is generally mentioned as the preferred concentration for the buffers (see page 7 line 2).

However, there is no particular pointer to citrate buffer at this concentration in D18, let alone in combination with specifically a sugar stabilizer and the further amounts of excipients required to achieve the claimed ratios of components. In more general terms, the limited experimental data in D18 on the stability of the compositions and on the variables affecting it, would not have assisted the skilled

person in its task of providing a "viable" adalimumab composition.

Moreover, the Board considers that the skilled person willing to solve the problem posed would have had knowledge of D3, which in contrast to D18 contains extensive experimental data on the factors affecting the stability of the compositions. As explained in detail above (under 4.2.9 to 4.2.11), the skilled person would therefore have been aware that citrate buffer requires specific conditions when willing to maintain stability. The skilled person would therefore not have modified the specific compositions of the examples of D18 by using citrate buffer at 10 mM, *i.e.* at a concentration corresponding to the presently claimed molar ratios, with a reasonable expectation to maintain the stability and thus provide an alternative composition.

4.3.4 In this context, contrary to the appellants' argument raised during oral proceedings, the above reasoning is not using D3 to "read" or "interpret" D18 in a particular manner not taught by D18 itself or to establish a technical prejudice. Taking into account the teaching of a secondary document when assessing inventive step is a standard approach and is not conditioned by the outcome of the reasoning (*i.e.* not limited to cases concluding to a lack of inventiveness).

4.3.5 Accordingly, the subject-matter of the main request meets the requirements of inventive step starting from D18 as the closest prior art.

4.4 Problem - solution approach starting from D2

4.4.1 D2 discloses adalimumab formulations, which are generally described as stable (see alternative compositions aiming at reducing aggregation of the antibody in D2, page 1). During oral proceedings the appellants concentrated on the formulation of example 73 as starting point. It was undisputed that the claimed formulation differed from this formulation of D2 in the nature and concentration of the buffer, *i.e.* citrate instead of acetate buffer at a lower concentration (20 mM in example 73 of D2).

4.4.2 The same reasoning regarding the formulation of the objective technical problem as starting from D3 and D18 applies *mutatis mutandis* (see 4.2.5 to 4.2.8). The objective technical problem to be solved resides therefore in the provision of an alternative adalimumab composition.

4.4.3 Similarly as starting from D18 and as argued by the appellants, the skilled person could in principle have modified the specific composition of example 73 of D2 by replacing the acetate buffer with a citrate buffer (citrate buffer being mentioned in a list of possible buffers on page 5, 4th paragraph of D2) at a lower concentration leading to the presently claimed molar ratios (the range of 10 mM to 20 mM is generally mentioned as the preferred concentration range for the buffers on page 5, 4th paragraph of D2).

However, in D2 all the specific examples of formulations containing a citrate buffer include a further stabiliser (arginine and/or cyclodextrin).

Moreover, the Board considers that the skilled person willing to solve the problem posed would have had knowledge of D3. As explained in detail above (under

4.2.9 to 4.2.11), the skilled person would therefore have been aware that citrate buffer requires specific conditions to maintain stability. The skilled person would therefore not have modified the specific compositions of example 73 of D2 by using citrate buffer at a lower concentration and in the absence of a further stabiliser with a reasonable expectation to maintain the stability and thus provide an alternative composition.

4.4.4 The comments made above under 4.3.4 apply *mutatis mutandis*.

4.4.5 Accordingly, the subject-matter of the main request meets the requirements of inventive step starting from D2 as the closest prior art.

4.5 Problem - solution approach starting from D1

4.5.1 The parties disagreed on the disclosure provided by D1. The appellants argued that D1 provided a concrete disclosure of a composition corresponding to Humira® with 10 mM citric acid as buffer based on:
- the general disclosure of adalimumab compositions provided on page 5 of D1, together with
- the disclosure of 1-10 mM citric acid buffer on page 6, and
- the fact that 50 mg/mL adalimumab represented the middle value of the disclosed concentration ranges, so that the skilled person would recognise that Humira® was itself a candidate composition to be modified.

4.5.2 This argument is not convincing. As detailed when assessing novelty over D1, the Board considers that D1 does not directly and unambiguously disclose a specific composition comprising adalimumab at the concentration

of 50 mg/mL, let alone together with the presently claimed molar ratios.

4.5.3 It follows that the claimed formulation differs from the general disclosure of D1 not only in the amount of mannitol (higher in the claimed composition) as argued by the appellants, but also by the selection of the appropriate amounts of adalimumab and of the corresponding excipients (including the citric acid buffer) to fulfil the presently claimed molar ratios.

4.5.4 The same reasoning regarding the formulation of the objective technical problem as starting from D3, D18 and D2 applies *mutatis mutandis* (see 4.2.5 to 4.2.8). The objective technical problem to be solved resides therefore in the provision of an alternative adalimumab composition.

4.5.5 As stated by the respondent, despite providing a list of suitable buffers to be used to formulate antibodies such as adalimumab, D1 indicates that the stability of the antibody depends on both the type and the concentration of a buffering agent (see summary and page 3, 2nd full paragraph, 1st sentence) and that the antibody concentration, the pH of the formulation and the selection of a suitable stabilizer and surfactant are further important parameters (see e.g. paragraph bridging pages 2 and 3). The skilled person would therefore not have found any indication in D1 towards a reasonable expectation of maintaining a stable composition by selecting the citrate buffer at 10 mM and increasing the amount of mannitol, while appropriately selecting the concentration of adalimumab and the other excipients so as to fulfil the claimed molar ratios.

4.5.6 Moreover, the Board considers that the skilled person willing to solve the problem posed would have had knowledge of D3. As explained in detail above (under 4.2.9 to 4.2.11), the skilled person would therefore have been aware that citrate buffer requires specific concentration conditions when willing to maintain stability, thus confirming the statement of D1 that the concentration of the buffer is important. It follows that the skilled person would not have applied a concentration of 10 mM citric acid with a reasonable expectation to maintain the stability compared to Humira®, let alone together with increasing the amount of mannitol and appropriately selecting the amounts of the other components.

4.5.7 The comments made above under 4.3.4 apply *mutatis mutandis*.

4.5.8 Accordingly, the subject-matter of the main request meets the requirements of inventive step starting from D1 as the closest prior art.

4.6 Problem - solution approach starting from D4

4.6.1 Starting from D4 as closest prior art, it was undisputed that the distinguishing feature resided in the nature of the buffer system used (mixture of citrate and phosphate buffer in Humira® in D4 and only citrate buffer in the present compositions) and in the amount of mannitol.

4.6.2 All parties defined the objective technical problem as the provision of an alternative adalimumab composition.

4.6.3 Contrary to the opinion of the appellants, the Board considers that the skilled person would not have

removed the phosphate buffer based on the disclosure of D4 combined with D8. The drawbacks of phosphate buffer in D8 underlined by the appellants are linked to the freezing of the formulation. D4 recommends avoiding such freezing (see paragraph "Storage and Stability"), so that these drawbacks (potential crystallization of phosphate buffer and thus pH variation) would not occur with the formulation of D4.

4.6.4 Furthermore, even if the skilled person would have removed the phosphate buffer, the same issue with the remaining sole citrate buffer as in the previous cases would apply. The skilled person would have learned from D3 that citrate buffer is not an universal buffer for adalimumab, which can be used under any conditions. The skilled person would hence have been aware that in the case of citrate buffer, its concentration as well as the one of the excipients cannot be modified arbitrarily with the expectation of maintaining the stability of the composition compared to Humira®. The skilled person would therefore not have arrived at the present adalimumab composition containing as sole buffer a citrate buffer and with the molar ratios of adalimumab to the buffer and to the mannitol as defined in present claim 1.

4.6.5 The comments made above under 4.3.4 apply *mutatis mutandis*.

4.6.6 It follows that the subject-matter of the main request is inventive starting from D4 as closest prior art.

4.7 Conclusion on inventive step

Accordingly, the ground of opposition under Article 100(a) EPC in combination with Article 56 EPC does not prejudice the maintenance of the patent.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated