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Datasheet for the decision of 11 December 2018

Case Number: T 0159/16 - 3.3.07

Application Number: 08866971.8

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Language of the proceedings: EN

Title of invention:
HIGH CONCENTRATION ANTIBODY-CONTAINING LIQUID FORMULATION

Patent Proprietor:
Chugai Seiyaku Kabushiki Kaisha
F. Hoffmann-La Roche AG

Opponent:
Glaxo Group Limited

Headword:
High Concentration Antibody Formulation / CHUGAI

Relevant legal provisions:
EPC Art. 100(a), 100(b), 100(c)

Keyword:
Inventive step - main request (no) - auxiliary request (yes)
Amendments - intermediate generalisation

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Case Number: T 0159/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 December 2018

Appellant: (Opponent)	Glaxo Group Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
Representative:	Bhogal, Jasber Kaur GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
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Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 25 November 2015 concerning maintenance of the European Patent No. 2238985 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	E. Duval
	C. Schmidt

Summary of Facts and Submissions

I. European patent No. 2 238 985 was granted on the basis of 21 claims. Independent claim 1 read as follows:

"A stable antibody-containing liquid formulation comprising 40 to 1000 mM arginine and 10 to 200 mM methionine."

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

III. The following documents were among those cited during the first-instance proceedings:

D2: WO 2004/091658
D5: WO 2007/124299
D6: WO 2007/109221
D7: Carpenter and Manning (Ed.) ; Rational Design of Stable Protein Formulations (2002); Practical Approaches to Protein Formulation Development (Chapter 1) B.S. Chang and S. Hershenson p.1-25 ; and High Throughput Formulation (Chapter 8) R. Nayar and M.C. Manning p. 177-199
D8: Daugherty and Mrsny, "Formulation and delivery issues for monoclonal antibody therapeutics", Advanced Drug Delivery Reviews 58, 2006, 686-706
D9: Lam XM et al., "Antioxidants for prevention of Methionine oxidation in recombinant monoclonal antibody Her2", Journal of Pharmaceutical Sciences 86 (11), 1997, 1250-5

D10: Chugai Pharmaceutical Co., Ltd Press Release, 24 May 2013
D12: Declaration of Yoshimi Imaeda
D20: WO 2001/024814
D22: Gokarn et al., 2006 Chapter 17 Excipient for Protein Drugs In. Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems, First Edition Ed. Katdare & Chaubal
D23: US 2003/0190316

IV. On 25 November 2015, the opposition division issued an interlocutory decision according to which, taking into consideration the amendments made by the proprietor during the opposition proceedings, the patent met the requirements of the EPC. The decision was based on the main request filed (initially as auxiliary request 2) by letter dated 23 June 2015.

The decision of the opposition division, as far as relevant for the present decision, may be summarised as follows:

(a) The main request met the requirements of Article 123(2) EPC, claim 1 in particular deriving from a combination of claims 1 and 6 together with paragraph 35 of the application as filed.

(b) The subject-matter of the main request met the requirement of sufficiency of disclosure: the opponent had not sufficiently demonstrated that the claimed stability was not achieved.

(c) The subject-matter of the main request was novel as it differed from the teaching of D5 by the antibody concentration, and from D6 by a combination of

several selections which the skilled reader would not seriously contemplate.

(d) The claimed subject-matter differed from the formulations of the closest prior art D2 by the presence of methionine; this resulted in an improved stability against dimerization. Since the prior art (D6, D8, D9) did not hint at this effect, the requirements of Article 56 EPC were fulfilled.

V. The opponent (appellant) lodged an appeal against that decision. With the statement setting out the grounds of appeal, the appellant contested the decision with respect to added subject-matter, sufficiency of disclosure, novelty and inventive step.

The following documents were filed with the statement of grounds of appeal:

D25: Vlasak and Ionescu, Current Pharmaceutical Biotechnology, 2008, 9, 468-481.

D26: Mahler, Journal of Pharmaceutical Sciences, Vol 98, NO. 9, 2009, 2909-2934.

VI. With the reply to the statement setting out the grounds of appeal, the patent proprietors (respondents) filed, in addition to the main request on which basis the decision under appeal was taken, six sets of claims as first to sixth auxiliary requests. The respondents also requested the Board not to admit document D26 into the proceedings.

VII. On 22 October 2018, the Board issued a communication pursuant to Article 15(1) RPBA.

Regarding the main request and auxiliary request 1, claim 1 was considered to comply with the requirements of Article 123(2) EPC. The Board furthermore construed claim 1 as requiring the formulation to be stable but not necessarily to exhibit an improved stability, such that the criteria of sufficiency of disclosure were met. The features of claim 1 were not seen as being disclosed in combination in D6, the requirements of novelty were accordingly fulfilled. However, the claimed subject-matter did not appear to involve an inventive step over the closest prior art D2 in combination with D6.

The limitations introduced by auxiliary requests 2-6 did not appear to overcome the objection of lack of inventive step. Additionally, the Board expressed doubts as to compliance with the criteria of Article 123(2) EPC for some dependent claims in auxiliary requests 2, 3 and 6, as well as for claim 1 of auxiliary requests 3-5.

VIII. By letter dated 9 November 2018, the respondents filed a revised main request and auxiliary requests 1-6.

Claim 1 of the main request read as follows:
"A stable antibody-containing liquid formulation comprising at least 120 mg/ml antibody, 100 to 300 mM arginine and 10 to 50 mM methionine".

Claim 1 of auxiliary request 1 differed from claim 1 of the main request by the following additional feature:
"the antibody is an anti-IL-6 receptor antibody".

Claim 1 of auxiliary request 2 differed from claim 1 of the main request by the following additional feature:

"wherein the antibody is the humanized anti-IL-6 receptor antibody MRA".

Claim 1 of auxiliary request 3 read as follows:
"A stable antibody-containing liquid formulation comprising 180 mg/ml antibody, 100 mM arginine and 30 mM methionine, wherein the antibody is the humanized anti-IL-6 receptor antibody MRA".

Claim 1 of auxiliary request 4 read as follows:
"A stable antibody-containing liquid formulation comprising 180 mg/ml of the humanized anti-IL-6 receptor antibody MRA, 100 mM arginine and 30 mM methionine, 0.5 mg/ml polysorbate 80, 20 mM histidine buffer solution, and having a pH of 6.0".

Claim 1 of auxiliary requests 5 and 6 were further limited, as compared with claim 1 of auxiliary request 4, in that the formulation was, respectively, "substantially composed of" and "consisting of" the same components.

IX. By letter dated 12 November 2018, the appellant maintained its objections with regard to added subject-matter, insufficiency of disclosure, lack of novelty and inventive step against the main request and auxiliary requests 1-6.

X. Oral proceedings were held on 11 December 2018.

XI. The appellant's arguments, as far as relevant to the present decision, may be summarised as follows:

(a) None of the requests met the requirement of Article 123(2) EPC. In particular, auxiliary request 3 resulted from an intermediate generalisation from

the examples A8 and A26, whereby the claimed features had been isolated from the amount of polysorbate, amount of histidine and pH common to all other formulations in the examples. The claimed features could not be said to be not so closely associated with the other features of the example. As to auxiliary request 4, the expression "comprising" was also held to constitute an unallowable intermediate generalisation.

(b) The subject-matter of claim 1 of the main request and its dependent claims lacked novelty over D6. Claim 30 of D6, in combination with pages 4 and 24, disclosed all claimed features without there being a need for multiple selections.

(c) The requirements of Article 100(b) EPC was not met: taking into account statements made by the opposition division and the patent proprietors, the invention was characterised by an inhibition of dimerization and deamidation during long term storage, or by the possibility to achieve the same stability with a lower total amount of excipients. A critical analysis of the data on file showed that none of these aspects had been sufficiently disclosed. More particularly, regarding deamidation, D25 showed that the pre-peak measured in the experimental data of the patent in suit could equally be explained by other acidic modifications, so that no conclusion regarding deamidation could be drawn therefrom.

(d) The subject-matter of the main request did not involve an inventive step over a combination of the closest prior art D2 with D6. D2 disclosed the combined presence of arginine and methionine in

antibody formulations, from which the claimed subject-matter differed only by the amount of methionine. The ensuing stabilization against aggregation was derivable from D6. Knowing that different mechanisms explained the degradation of the formulation, the skilled person would be prompted to combine arginine and methionine. Neither the reduced total amount of excipients nor any over-proportionality or synergistic effect could be considered in the formulation of the technical problem. The subject-matter of auxiliary requests 1-6 was likewise considered obvious. Objections were alternatively raised over a combination of D2 with D5, D9 or D20, or based on D5 or D20 as closest prior art in combination with common general knowledge, D6 or D23.

XII. The respondents' arguments, as far as relevant to the present decision, may be summarised as follows:

(a) The requirements of Article 123(2) EPC were met. In particular, auxiliary requests 3-5 resulted from allowable intermediate generalisations starting from samples A8 and A26. The application as filed taught that the essential features of the invention were those of claim 1 of the application as filed, while the other components could be varied. The possibility that further components be present in the formulation was indicated in paragraph [0045]. Alternatively said auxiliary requests could be seen as a combination of the preferred embodiments in the preferred amounts.

(b) The claimed invention was sufficiently disclosed. The claimed formulations were stable according to the definition provided in the description in

paragraph [0038]. The analytical method used to measure deamidation was confirmed in D25 to be suitable for antibody analysis.

(c) The combination of features of claim 1 of the main request was not disclosed in D6 as it resulted from several selections which the skilled person would not contemplate.

(d) In respect of the main request, D2 was best suited as closest prior art. D2 however did not disclose formulations comprising both arginine and methionine. The claimed subject-matter differed from D2 in that it contains 10-50 mM methionine in addition to the arginine. This resulted in an over-proportional reduction of aggregation and deamidation, which could be regarded as a synergistic effect. This over-proportional effect was not hinted at in D6, which should be seen as limited to low concentration antibody formulations. On the contrary, D5 and D20 taught away from high concentrations of methionine in addition to arginine. There was also no incentive for the skilled person to combine methionine with arginine rather than replace one with the other.

(e) In respect of auxiliary requests 1 and 2, it was further argued that different antibodies required different stabilisations, such that the skilled person would have no reasonable expectation that methionine would successfully stabilise anti-IL-6-receptor or MRA antibodies. The commercial success of Actemra, having a shelf life of 2 years, further supported the existence of an inventive step for the auxiliary requests focusing on examples A8 and A26.

XIII. The appellant requested that the decision under appeal be set aside and that the European patent No. 2 238 985 be revoked.

XIV. The respondents requested that the appeal be dismissed and that the patent be maintained on the basis of the main request or one of auxiliary requests 1 to 6, all requests filed by letter dated 9 November 2018.

Reasons for the Decision

Main request

1. Inventive step

1.1 The Board, in agreement with both parties, considers D2 as a suitable starting for the assessment of inventive step. D2 is concerned with the provision of stable, highly concentrated antibody formulations.

D2 discloses (see claims 1 and 6; example 1) a stable liquid formulation comprising a protein or antibody in an amount of 100-260 mg/ml, e.g. 150 mg/ml, 50-200 mM arginine.HCl, 10-100 mM histidine, polysorbate (e.g. polysorbate 80, see page 51, line 27) in an amount of 0.01-0.1%, and having a pH of 5.5-7.0. However, the formulation of example 1 of D2 does not contain methionine.

D2 generally mentions the optional presence (see page 50, line 11), in the liquid formulation, of methionine as an antioxidant. However no amount is specified for methionine. Furthermore, D2 does not show formulations comprising both methionine and antibody, as this would

require several selections starting from the general teaching of D2 (antibody as the protein, methionine as the additive). No general preference for the presence of methionine over the other additives considered on pages 50-51 can be derived from D2; despite the mention of methionine as a promising antioxidant in D22 (see page 299), it cannot be concluded that this alternative in D2 would be the only one considered by the skilled person.

1.2 The subject-matter of claim 1 thus differs from the formulations of D2 by the presence of 10-50 mM methionine.

1.3 For the Board, this differentiating feature leads to the following technical effect:

1.3.1 The patent in suit credibly shows that the presence of 10-50 mM methionine leads to an improved stabilisation against dimerisation: in heat-accelerated assays (patent in suit, example 1) and light accelerated assays (ibid., example 3), a comparison of formulations which are identical with respect to antibody, arginine and additives contents, and differing only by the presence of methionine (example 1, table 1, sample A3 vs. samples A7-A9; example 3, table 3, sample A21 vs. samples A25 and A26) shows an improvement in respect of dimer formation, as measured by gel permeation chromatography (SEC, see [0066]-[0069]). The same conclusion can be drawn from document D12: a comparison of the control and +Met samples, differing only by the additional presence of 50 mM methionine, show an effect on aggregation (i.e dimerisation, the two expressions referring here to the same problem).

1.3.2 However, the Board does not share the respondents' opinion that these data reflect a synergistic or over-proportional effect resulting from the combined presence of arginine and methionine.

Arginine and methionine can only be considered to interact synergistically if their combination leads to an additional effect that goes beyond the sum of the effects of each component taken in isolation. In the present case, the absence of data showing the effect of methionine alone on dimerisation makes it impossible to compare the combined effect of methionine and arginine with the respective effects of methionine alone and arginine alone. Likewise, it is not demonstrated that the combined effect of methionine and arginine is over-proportionally greater than the effect of methionine alone. Rather than demonstrating that arginine and methionine act in a synergistic manner, the data presented may more simply be explained by a greater stabilising activity of methionine as compared with that of arginine.

1.3.3 For the Board, an effect of methionine on stabilisation against deamidation can also not be considered for the definition of the technical problem.

In the patent in suit, deamidation is quantified by measuring the total amount of pre-peak by ion-exchange chromatography (IEC, see [0080]-[0081], using a Dionex ProPac WCX-10 column). As evidenced by the review D25 (see page 470), this technique is well established for antibody analysis; although the possibility exists that the pre-peaks include other acidic degradation products beside deamidation, as shown in D25 (see table 1 page 470), the appellant has not convincingly disproved the statement in the patent in suit (see [0080]) that the

degradation products are mainly deamidation products. This measurement technique can therefore be accepted as a reliable method for assessing the level of deamidation.

The effect of arginine and methionine on antibody deamidation is assessed in heat-accelerated assays (see example 2, table 2) and light accelerated assays (see example 3, table 4). However none of the samples of example 2 contain arginine and methionine in combination; these samples thus do not reflect the invention. As to example 4 (see Figure 8), the improved stabilisation against deamidation alleged by the respondents does not arise with a methionine amount of 10 mM. As a result, this purported effect does not arise over the whole scope of the claimed range, namely 10-50 mM.

1.3.4 Lastly, the reduction of the amount of excipients in the antibody formulation cannot be considered as such in the definition of the technical problem, since this does nor constitute a differentiating feature of the claim over the closest prior art D2.

1.4 The objective technical problem may consequently be seen as the provision of liquid formulations with high antibody concentrations, exhibiting improved stability against dimerisation. For the reasons indicated above, the Board is satisfied that the claimed formulations are a solution to the problem.

1.5 D6 discloses a method for reducing aggregation of proteins, e.g. antibodies, in liquid formulations (see abstract and page 4), comprising adding methionine to the formulation. The concentration of methionine in D6 is 0.5-50 mM (see claim 29), a concentration of 10 mM

being used in the examples. D6 shows that methionine is effective at reducing antibody aggregation.

Though the concentrations of antibody in examples 1-3 of D6 are much lower than the claimed content of at least 120 mg/ml, the general teaching of D6 (see pages 4 and 24) covers concentrations up to 300 mg/ml. The problem of protein aggregation may be emphasised by high protein concentrations but cannot be regarded as being specific to such high concentrations, if only for the reason that D6 explicitly addresses this problem. Accordingly, the Board cannot share the respondents' argument that D6 would not have made the suitability of methionine formulations for high concentrations plausible for the skilled reader.

The Board also notes that, just as the optional additional presence of methionine (as antioxidant) in the formulation is mentioned in D2, the optional additional presence of arginine is disclosed in D6 (see claim 30). Additionally, the Board shares the appellant's opinion that the skilled person, aware of the existence of different degradation pathways (see e.g. D22 page 293, or D7 page 9), would not consider that a choice must be made between either arginine or methionine, but rather that a combination of both is sensible so as to address the various potential degradation mechanisms.

The Board cannot see in D20 (see page 15, lines 15-19, and page 48) or D5 (see page 19, lines 4-8) the demonstration of a prejudice against high levels of methionine, firstly because these patent documents do not reflect the common general knowledge, and secondly because neither D5 nor D20 actually state that the presence of e.g. 10 mM methionine is detrimental.

Consequently the skilled person, seeking to further improve on the stabilising effect of arginine with respect to dimerisation / aggregation known from D2, is prompted by D6 to add methionine to the formulation, in the claimed amounts, to solve the problem.

This conclusion is not modified by the respondents' argument pertaining to the commercial success of Actemra: the related evidence D10, announcing the launch of this formulation for the treatment of rheumatoid arthritis, neither demonstrates the alleged commercial success nor shows that it derives from the technical features of the invention rather than from other causes.

1.6 Accordingly the main request does not fulfill the requirements of Article 56 EPC.

Auxiliary requests 1 and 2

2. Inventive step

2.1 In auxiliary requests 1 and 2, the antibody is limited respectively to an "anti-IL-6 receptor antibody" and to the "humanized anti-IL-6 receptor antibody MRA". As noted by the respondents, the antibody MRA is identical to the antibody hPM-1 known from D23 (see in this respect the examples of D23 and the description of the patent in suit, [0029]).

2.2 These limitations do not disqualify D2 as closest prior art: D2 is not limited in respect of the antibody and mentions that it may be one that binds to any of a list of molecules including interleukins IL-1 to IL-10 (see page 6, lines 30-31 and 19). As such, D2 appears to

remain a plausible starting point for the assessment of inventive step.

2.3 The subject-matter of claim 1 of each of auxiliary requests 1 and 2 differs from the formulations shown in D2 by the presence of 10-50 mM methionine and in that the antibody is, respectively, an anti-IL-6 receptor antibody or the humanized anti-IL-6 receptor antibody MRA.

2.4 The presence of the same additive in the same amounts (i.e. 10-50 mM methionine) can be associated with the same technical effect as for the main request (see 1.3 above), namely an improved stabilisation against aggregation. As to the choice of the particular antibody, the respondents did not submit that it led to any particular technical effect.

2.4.1 The technical problem may consequently be seen as the provision of liquid formulations with high anti-IL-6 receptor antibody or high MRA antibody concentrations, exhibiting improved stability against dimerisation. This problem is credibly solved by the claimed formulations.

2.5 The addition of methionine in the claimed amounts is, as explained above for the main request, shown in D6 as a solution to the same problem, namely an improved stability against aggregation. As to the choice of the antibody, whether it is any anti-IL-6-receptor antibody or MRA, it cannot involve an inventive as such antibodies are known e.g. from D23.

As pointed out by the respondents, it is known (see D8, pages 690, 692, 693, 697, 701; see also D23, where a different solution is proposed for the stabilisation of

MRA) that different antibodies require different stabilisations. However, the Board cannot share the respondents' position that these known antibody specificities in term of stabilisation needs would dissuade the skilled person to consider the claimed arginine methionine combination as suggested by documents D2 and D6, for lack of reasonable expectation of success. The concept of "reasonable expectation of success" does not apply when the implementation and the testing of an approach suggested by the prior art does not involve any particular technical difficulties. The Board holds that this is the case for the present invention, relating to the proper choice of the additives in the formulation of known antibodies. In such a situation, the skilled person will prefer to verify whether the potential solution suggested by D2 and D6 would work, rather than abandon the project because success was not certain.

2.6 Accordingly, auxiliary requests 1 and 2 do not comply with the requirements of Article 56 EPC.

Auxiliary request 3

3. Article 123(2) EPC

As compared with the main request, claim 1 of auxiliary request 3 was limited in respect of the nature and amount of antibody (180 mg/ml MRA antibody), amount of arginine (100 mM) and amount of methionine (30 mM). These features are disclosed in samples A8 and A26 of the application as filed, where, however, they appear in combination with further features, namely the presence of 0.5 mg/ml polysorbate 80 and 20 mM histidine buffer solution, as well as a pH of 6.0. The question thus arises whether this intermediate

generalisation introduces added subject-matter, or whether the skilled man could have readily recognised the features pertaining to antibody, arginine and methionine as not so closely associated with the other features of samples A8 and A26 as to determine the effect of these embodiments as a whole in a unique manner and to a significant degree.

The Board notes that all the examples are characterised by the presence of 0.5 mg/ml polysorbate 80 and 20 mM histidine buffer solution, as well as a pH of 6.0. Consequently, the examples do not disclose that these further additives and pH may be varied without effect on the formulation stability. Furthermore, the application as filed does not assign any role to the polysorbate surfactant (see [0039]), such that the skilled person cannot exclude a contribution of said surfactant to the formulation stability. The condition for isolating the amounts of antibody, arginine and methionine from the further features of samples A8 and A26 are thus not met.

The amendments cannot be seen either as a limitation of the original generic disclosure using the most preferred embodiments or values. The amount of 30 mM methionine in particular appears only in the examples, such that this argument still supposes that the feature be isolated from the examples.

Accordingly auxiliary request 3 does not fulfill the criteria of Article 123(2) EPC.

Auxiliary request 4

4. Article 123(2) EPC

Claim 1 of auxiliary request 4 recites all the components, in their respective amounts, of samples A8 and A26 of the application as filed, namely 180 mg/ml MRA antibody, 100 mM arginine and 30 mM methionine, 0.5 mg/ml polysorbate 80, 20 mM histidine buffer solution, as well as a pH of 6.0. Although said examples are "closed" compositions consisting of the stated components, no added subject-matter is introduced, in the present case, by retaining the open-ended expression "comprising" of claim 1 as filed: as pointed out by the respondents, the application as filed indicates that the formulation may generally contain further components (see [0045]).

Accordingly, the requirements of Article 123(2) EPC are met.

5. Sufficiency of disclosure

Regarding sufficiency of disclosure, no specific arguments were put forward with respect to auxiliary request 4 and the appellant relied on its written submissions. The Board remains of the opinion, explained in the communication pursuant to Article 15(1) RPBA (see Point 3.), that the claimed invention is sufficiently disclosed: the feature of claim 1, according to which the formulation should be stable, cannot be construed such that it requires the formulation to exhibit an *improved* stability over any reference formulation. No evidence was adduced by the appellant to show that the claimed formulations,

corresponding to samples A8 and A26 of the patent, fail to exhibit the claimed stability.

Accordingly the requirements of sufficiency of disclosure are fulfilled.

6. Novelty

The appellant maintained its objection of lack of novelty of the main request over D6; during oral proceedings, however, the appellant did not specifically comment on novelty of the more narrowly defined subject-matter of auxiliary request 4, but rather announced that it relied on its written submissions.

The Board first notes that D6 does not disclose the humanized anti-IL-6 receptor antibody MRA specified by claim 1 of the auxiliary request 4. Furthermore, the Board remains of the opinion (expressed with respect to the main request) that, in order to arrive at the claimed subject-matter, several selections must be made in respect of the protein (an antibody being but one alternative in claims 29-30), of the second amino acid (arginine), and in respect of the amounts for the respective components (see Point 4. of the communication pursuant to Article 15(1) RPBA); this applies all the more to auxiliary request 4, where these amounts are limited to single values.

As a result, auxiliary request 4 fulfills the requirement of novelty.

7. Inventive step

7.1 Starting from the formulations of D2 as closest prior art, the claimed subject-matter differs *inter alia* by the presence of 30 mM methionine.

7.2 This differentiating feature leads not only to an improved stabilisation against dimerisation, as explained above (see 1.3.1), but also to an improved stabilisation against deamidation, for the following reasons:

As explained above (see 1.3.3), a measurement of the total amount of pre-peak in ion-exchange chromatography can be accepted as a reliable method for assessing the level of deamidation. Using this measurement method, an effect of methionine on antibody deamidation is shown to occur in light accelerated assays for the claimed amount of 30 mM (see example 3, Figure 8 and table 4). Additionally, the Board notes that this result contrasts with the absence of effect of methionine alone or arginine alone on deamidation in heat-accelerated assays (see example 2, table 2).

7.3 The objective technical problem may consequently be seen as the provision of liquid formulations with high MRA antibody concentrations, exhibiting improved stability against both dimerisation and deamidation.

7.4 D6 is silent about any effect of methionine on deamidation. Considering the range of possible additives which may be added to stabilise the formulation against aggregation, the demonstrated effect of methionine on deamidation cannot be seen as a bonus effect. While the antioxidant activity of methionine is known, its effect on deamidation is not

derivable from D5, D9 or D20 either. The alternative objection based on D5 or D20 as closest prior art does not alter this outcome, since D5 and D20 are less suitable starting points for the assessment of inventive step (since they do not related to high concentration anti-IL-6-receptor antibody formulation) and because it remains the case that the effect of methionine on deamidation could not be anticipated by the skilled person.

7.5 For these reasons, the subject-matter of auxiliary request 4 involves an inventive step as required by Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Opposition Division with the order to maintain the patent on the basis of the fourth auxiliary request, filed with letter dated 9 November 2018 and a description to be adapted.

The Registrar: The Chairman:

B. Atienza Vivancos J. Riolo

Decision electronically authenticated