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Datasheet for the decision of 21 June 2022

Case Number: T 2342/19 - 3.3.07

Application Number: 14742093.9

Publication Number: 3013318

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Language of the proceedings: EN

Title of invention:
STABLE LIQUID FORMULATION OF AMG 416 (VELCALCETIDE)

Patent Proprietor:
Amgen Inc.

Opponent:
Hexal AG

Headword:
Liquid formulation of AMG 416/AMGEN

Relevant legal provisions:
EPC Art. 115, 114(2), 100(a), 56
RPBA 2020 Art. 13(2)

Keyword:
Observations by third parties - admitted (no)
Inventive step - (yes)

Decisions cited:
T 1214/17

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 2342/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 June 2022

Appellant: (Opponent)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320 (US)
Representative:	Dörries, Hans Ulrich df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 June 2019 rejecting the opposition filed against European patent No. 3013318 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	A. Jimenez

Summary of Facts and Submissions

I. European patent 3 013 318 (hereinafter "the patent") was granted on the basis of 15 claims. The independent claims of the patent as granted read as follows:

"1. A pharmaceutical formulation comprising AMG 416 in aqueous solution, wherein the formulation has a pH of 2.0 to 5.0."

"15. A formulation comprising 2 mg/mL to 20 mg/mL of AMG 416 in aqueous solution, a succinate buffer that maintains the formulation at a pH of about 3.0 to 3.5, and a sufficient concentration of sodium chloride for the formulation to be approximately isotonic."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step.

III. The opposition division took the decision to reject the opposition.

IV. The decision of the opposition division, posted on 21 June 2019, cited *inter alia* the following documents:

D1: WO 2012/170955 A1
D2: S. Frokjaer and L Hovgaard (Eds.), "Pharmaceutical Formulation Development of Peptides and Proteins", Taylor & Francis, 2000, pp. 145-155
D3: L. Lachman *et al.*, "The Theory and Practice of Industrial Pharmacy", Varghese Publishing House, Bombay, 3rd edition, 1987, pp. 190-195 and 764-768

D5: H. Feltkamp *et al.*, "Pharmazeutische Qualitatskontrolle", Georg Thieme Verlag Stuttgart New York, 1983, pp. 502-504
D6: Aulton's Pharmaceutics, 3rd edition, Churchill Livingstone Elsevier, 2007, pp. 8, 368-369 and 616-620
D7: K. H. Bauer, K.-H. Frömming, C. Führer "Lehrbuch der Pharmazeutischen Technologie", Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2006, pp. 238-243
D8: Y.-C. J. Wang and M. A. Hanson, "Parenteral Formulations of Proteins and Peptides: Stability and Stabilizers", Journal of Parenteral Science and Technology, 1988, Supplement Vol. 42, S4-S26
D14: WO 2011/014707 A2
D15: Post-filing data from Amgen concerning the stability of aqueous solutions comprising AMG 416
D19: B.S. Chang *et al.*, "Lyophilized Biologics" in "Lyophilized Biologics and Vaccines", Springer, 2015, pp. 93-119
D20: Wong *et al.*, Advanced Drug Delivery Reviews, 2008, 60(8), pp. 939-954;
D21: K. Wasan (Ed.), "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Discovery", John Wiley & Sons, Inc., 2007, "Chapter 4: Principles in the Development of Intravenous Lipid Emulsions", pp. 88-123

V. The opposition division decided in particular as follows:

The difference between the claimed subject-matter and the one disclosed in the closest prior art D1 resided in the formulation of AMG 416 in the form of an aqueous solution having a pH of 2.0 to 5.0. The resulting technical effects were an improved ease of use and a high storage stability. The objective technical problem to be solved was thus the provision of a formulation more convenient to use and having a high degree of

stability for an extended period of time. The solutions claimed in independent claims 1 and 15 were not obvious in light of the prior art.

VI. The opponent (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the appellant's statement setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1-17 filed therewith, wherein auxiliary requests 1-6 and 7-13 were originally filed during the first instance proceedings on 11 June 2018 and 25 April 2019, respectively.

VIII. Third party observations were filed on 31 January 2022 together with 5 documents (HW1 to HW5):

HW1: Walter *et al.*, J Pharmacol Exp Ther, Fast Forward, 2013, DOI:10.1124/jpet.113.204834
HW2: Journal of Parenteral Science and Technology, 1988, Supplement Volume 42 Number 2S, technical report No. 10, "Parenteral Formulations of Proteins and peptides: Stability and Stabilizers", pages S1-S26
HW3: Christina Avanti, Thesis, "Innovative Strategies For Stabilization of Therapeutic Peptides in Aqueous Formulations", 2012, pages 1-33
HW4: Pharmaceutical Dosage Forms, Parenteral medications, Third Edition, Volume 1, Formulation and Packaging, 2010, Chapter 9, pages 222-253
HW5: Pharmazeutische Technologie, 1993, Kapitel 9, Seiten 225-228

IX. Oral proceedings were held before the Board on 21 June 2022.

X. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

XI. The respondent requested that the appeal be dismissed or, in the alternative, that the patent be maintained on the basis of one of auxiliary requests 1-17 filed with the reply to the statement setting out the grounds of appeal.

The respondent also requested the third party observations filed on 31 January 2022 and the accompanying documents HW1 to HW5 not to be admitted into the appeal proceedings or not to be considered by the Board.

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

(a) The appellant had no comment regarding the issue of admittance of the third party observations and the accompanying documents in the appeal proceedings.

(b) The closest prior art D1 disclosed intravenously administered AMG 416 formulations. In light of common general knowledge, these formulations were necessarily aqueous. The distinguishing feature was therefore only the specific pH of the solution. The data provided in the patent and in D15 did not substantiate any improved effect compared to the formulations of D1. Even if it would be considered that an improved stability had been obtained, this effect had not been shown over the whole claimed range. The objective technical problem resided therefore in an alternative formulation of AMG 416 to be administered intravenously and, for the sake

of argumentation, having higher storage stability. The provision of an aqueous solution as ready-to-use formulation would be obvious in view of paragraph [085] of D1. Furthermore, in view of common general knowledge as revealed by D2, D3, D7, D8 and D19, the first stage of active ingredient formulation development would be the formulation as an aqueous solution. This would also apply when the active ingredient was a peptide. pH stability study would be the first routine test performed in this approach. When carrying out such routine experiments, the skilled person would inevitably have arrived at the present pH range. The subject-matter of the granted claims was therefore not inventive.

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

(a) The third party observations and the accompanying documents were not to be admitted because they were lated-filed and no reasons justifying the existence of exceptional circumstances for their late filing had ben provided.

(b) The granted claims met the requirements of Article 56 EPC. Starting from D1 as closest prior art, the distinguishing features were the formulation as an aqueous solution and the specific pH thereof. It was indeed not compulsory for intravenous formulations to be aqueous solutions. The data in the patent as well as D15 substantiated that the claimed formulations had improved storage stability. The objective technical problem as formulated during oral proceedings resided in the provision of an AMG 416 formulation having storage

stability over an extended period of time. The formulation of peptides was generally known as involving complex stability issues. None of the cited prior art documents would have motivated the skilled person to prepare an aqueous solution of AMG 416 having a pH of 2.0 to 5.0 to obtain a storage stable formulation with a reasonable expectation of success.

Reasons for the Decision

1. Admittance of third party observations

1.1 The third party observations and accompanying documents HW1 to HW5 were submitted under Article 115 EPC on 31 January 2022, *i.e.* after notification of the summons to oral proceedings dated 12 July 2021.

1.2 According to established case law, the admittance of third-party observations filed after the time limit under Article 99(1) EPC is subject to the same criteria as the admission of late filed submissions within the meaning of Article 114 (2) EPC (see the Case Law of the Boards of Appeal, 9th edition, 2019, III.N.4.4). Hence, the Board has discretion to take such observations into consideration or to disregard them, taking into account the same criteria as for late-filed submissions by parties under the Rules of Procedure of the Boards of Appeal (RPBA). It follows that, in the present case, the admission of the third party observations are to be assessed using the criteria of Article 13(2) RPBA 2020.

1.3 Pursuant to Article 13(2) RPBA 2020, these submissions shall not be admitted unless there are exceptional circumstances which have been justified with cogent reasons by the third party.

1.4 The third party has not provided any reason for filing the observations and the accompanying documents at this late stage of the proceedings.

1.5 The objections of lack of novelty and inventive step raised in the third party observations are based on newly filed documents HW1 to HW5 and constitute an entirely fresh case. Furthermore, the documents HW1 to HW5 have been available for a long time (HW1 is a non-patent literature document published in 2013 and HW2 to HW5 are abstracts of books, all published even before the notice of opposition was filed). Moreover the disclosure of HW1 to HW5 does *prima facie* not appear to be more relevant to the case than the one of the documents already included in the proceedings. The disclosure of HW1 regarding the vehicle used for AMG 416 and the final pH is ambiguous and the date of public availability of HW1 has been questioned by the respondent. HW2 to HW5 relate to possible degradation reactions for peptides in general, *i.e.* not specifically for AMG 416, and two of them were already cited in the proceedings. The Board cannot therefore identify any exceptional circumstances which would justify the admittance of the third party observations.

1.6 Accordingly, the third party observations and the accompanying documents are not admitted into the appeal proceedings.

Main request - patent as granted

2. Novelty

During the appeal proceedings the appellant did not pursue its objection of lack of novelty. The Board

agrees with the opposition division that the ground of appeal according to Article 100(a) EPC in combination with Article 54 EPC does not prejudice the maintenance of the patent as granted.

3. Inventive step

3.1 Closest prior art

3.1.1 The patent in suit relates to a liquid formulation of AMG 416, a peptide agonist of the calcium sensing receptor useful in the treatment of secondary hyperparathyroidism (see paragraphs [0002] and [0004]). The purpose of the patent is to provide a liquid formulation thereof which remains nevertheless stable upon storage for an extended period of time (see paragraph [0006]).

3.1.2 In agreements with both parties, the Board considers D1 to represent the closest prior art.

3.1.3 D1 discloses inter alia the present peptide (see Ac-c(C)arrrar-NH_2 (SEQ ID N0:3)), for use in the treatment of secondary hyperparathyroidism in dialysis patients (see for example paragraphs [001], [021], [028], [033], [084]). In particular examples 1 and 2 of D1 describe the intravenous administration of AMG 416.

3.2 Distinguishing features

3.2.1 The closest embodiments of D1, *i.e.* examples 1 and 2, do not provide any information regarding the actual formulation of the peptide. In particular, it was undisputed that no information regarding the pH was provided. According to the appellant, it would be nevertheless implicit that the intravenous injection

required formulations in the form of an aqueous solution.

3.2.2 However, in view of D2, D6, D7, D14, D20 and D21 cited by both parties, no such general conclusion can be drawn. While D2, D6 and D7 may indicate that aqueous solution is the recommended formulation for intravenous injection (see D2, page 146, point 2; D6, page 8, right column, penultimate paragraph, penultimate sentence; D7, page 239, right column, lines 1-3), D20 and D21 substantiate that also emulsions and suspensions may be administered via intravenous injection (see D20, page 945, left column, third paragraph, page 951, left column, last paragraph; D21, Tables 4.1 and 4.2 on pages 89-90).

The fact that, as argued by the appellant, D20 and D21 relate primarily to poorly water soluble drugs and hydrophobic drugs does not undermine this teaching, especially in so far as D14 clearly states that peptides such as the presently claimed one may be formulated as aqueous and non-aqueous solutions but also emulsions or suspensions (see paragraph [0166]).

In this context, the appellant further argued that it would be difficult and thus not common to prepare AMG 416 nanosuspension and that only nanosuspensions could be administered intravenously while D1 generally mentioned suspensions (*i.e.* with potentially larger particles than nanosuspensions). While the disclosure of D1 is indeed general and does not specifically describe a nanosuspension of AMG 416, it does equally not disclose an aqueous solution thereof. It remains that according to D20 nanosuspensions are suitable for the intravenous administration of more complex molecules such as proteins (see page 951, right column,

last sentence), so that it would also be suitable for peptides.

It follows that the argument of the appellant that the formulation of AMG 416 in the examples of D1 necessarily has to be an aqueous formulation is not convincing.

3.2.3 Furthermore, the remaining parts of D1 do also not appear to provide an unambiguous teaching that AMG 416 intravenously administered in the examples was indeed formulated as an aqueous solution. In particular, paragraph [0085] mentions buffered or saline solutions as well as the reconstitution of a lyophilised active ingredient into a solution or a suspension. While a clear reference to the lyophilised salt of AMG 416 is made in the last sentence of the paragraph, no particular reconstitution form (solution or suspension) is specified and this is merely "one embodiment", *i.e.* it does not exclude any other formulation forms.

3.2.4 It cannot thus be concluded that in the specific examples 1 and 2 AMG 416 was administered in the form of an aqueous solution.

3.2.5 Accordingly, the subject-matter of claim 1 differs from the one of D1 in that the formulation of AMG 416 is limited to:
(i) an aqueous solution
(ii) having a pH of 2.0 to 5.0.

3.3 Technical effects and objective technical problem

3.3.1 The parties disagreed as to the technical effects linked to said distinguishing features.

3.3.2 According to the respondent, both distinguishing features were interrelated and the provision of an aqueous solution having the specific pH led to a ready-to-use formulation having storage stability over an extended period of time.

3.3.3 The appellant dealt with the effects of both differences separately.

Regarding the feature (i), the appellant explained that the provision of a ready-to-use solution could not be taken into account. This was because granted claim 1 was not limited to a ready-to-use solution and encompassed reconstituted solutions. Moreover, the disclosure of D1 was not limited to the lyophilised product and generally encompassed ready-to-use solutions.

Concerning feature (ii), during the written proceedings, the appellant argued that no comparison versus D1 had been performed. According to the appellant, as it was not stated in D1 that the formulation would be unstable, it could not be concluded that the present solution had an improved storage stability compared to D1. Furthermore, the appellant contested that an improved storage stability had been substantiated over the whole scope of the claims. It would have been substantiated only for a specific composition having *inter alia* a specific AMG 416 concentration and a specific pH. Furthermore, tables 1-3 and 6-7 of the patent in suit indicated that the stability decreased when the concentration of active ingredient increased, so that good stability would not be achievable at higher concentrations.

3.3.4 The Board notes that a ready-to-use formulation may be provided by the requirement in claim 1 that the formulation must be in the form of an aqueous solution (feature (i)).

Regarding feature (ii), the Board observes that the experimental data provided in table 5 of the patent in suit substantiate that solutions having a pH of 2 to 5 have an increased storage stability compared to solutions having a higher pH. The solutions at pH 6 degrade indeed earlier when the storage temperature and/or the AMG 416 concentration increase. A long term storage stability at 5°C for solutions having a pH in the presently claimed range (pH between 3.0 and 3.6) is furthermore experimentally substantiated by the data in D15. The results provided in D15 (submitted after filing of the present patent) do merely confirm the teaching of the patent and may thus be taken into account in the assessment of inventive step.

The storage stability (effect of feature (ii)) became actually a challenge due to the choice of a formulation in a ready-to-use form (effect of feature (i)). Hence, both distinguishing features are interrelated and cannot therefore be considered in a separated manner.

3.3.5 With respect to the concerns of the appellant on the achievement of an effect compared to D1 and over the entire claimed range, the Board notes the following:

(a) As stated above (see 3.2), D1 does not provide any unambiguous disclosure of the type of formulations injected in examples 1-2 nor any information regarding a potential storage thereof. It follows that the disclosure of D1 does not allow to perform any direct comparison. The present issue is to

determine whether the selection of an aqueous solution with the present pH range achieves a particular technical effect. Comparisons between various aqueous solutions differing from each other only in the pH value are thus appropriate in the present case to demonstrate an effect associated to the selected pH range for aqueous solutions. The results of table 5 are therefore relevant and indicate an improved storage stability within the claimed pH range.

(b) The data provided in the patent in suit indeed indicate that with increasing concentration of active ingredient, the storage stability thereof decreases. This would actually be expected by the person skilled in the art. Nevertheless, the provided data also show that for one given concentration, when the pH is within the claimed range, the degradation of the active ingredient is less important than at higher pH (see table 5). Hence the effect linked to the pH range remains. For higher concentration, high stability may be maintained over a shorter time period than for less concentrated solutions. This does however not mean that the effect linked to the pH of the aqueous solution is not observed.

(c) The fact that the granted claims encompass reconstituted solutions does not mean that there would be no technical effect compared to D1 for such embodiments. In view of the data provided in the patent in suit, it is indeed credible that, independently of its process of preparation (*i.e.* direct dissolution or reconstitution of lyophilised product), an aqueous solution of AMG 416 having a

pH in the present claimed range would have high storage stability.

3.3.6 Accordingly, starting from the examples 1-2 of D1, the objective technical problem resides in the provision of a ready-to-use formulation of AMG 416 having high storage stability.

3.3.7 In this context, the appellant argued during oral proceedings that the definition of the storage stability in absolute terms (*i.e.* as "high") would not be appropriate. As stated above, the level of stability may vary depending on the conditions (such as the concentration of the active ingredient, see above 3.3.3, last paragraph). A definition in relative terms (*i.e.* as "higher") should be used instead.

This argument is not convincing. As stated above (see 3.3.5 (a)), in the present case, due to the unspecific disclosure of the formulations in D1, it was not possible to demonstrate any direct improvement compared to D1. This is why, since the technical problem is formulated with regard to the closest prior art embodiment, no relative term can be used. Moreover the use of the term "high" does not mean that any particular level of stability has to be fulfilled. It provides a qualitative indication and hence translates the technical effect (*i.e.* that, for otherwise identical conditions, the storage stability achieved when using a pH in the claimed range is improved).

3.4 Obviousness of the solution

3.4.1 The idea of providing an aqueous solution of an active ingredient may appear obvious to the skilled person willing to provide a ready-to-use solution *per se*.

However, in the present case, the active ingredient is a peptide and the formulation of peptides in aqueous solution is known to possibly be challenging due to stability issues (see for example D2 and D19, page 105 last full paragraph, last sentence).

3.4.2 The closest prior art D1 does further not provide any particular hint towards an aqueous solution of AMG 416. As already discussed above (see 3.2.1), no information is provided regarding the actual composition of the liquid formulation of examples 1-2. Paragraph [0085] of D1 mentions in general, *i.e.* for any of the compounds disclosed therein, buffered or saline solutions as well as the reconstitution of a lyophilised active ingredient into a solution or a suspension. The only more specific embodiment relating to AMG 416 is a lyophilized product (see last sentence of paragraph [0085]). In the present case, the skilled person willing to solve the problem posed would thus not have found in D1 any particular motivation to prepare specifically an aqueous solution of AMG 416, let alone with the presently claimed pH, with the expectation of obtaining a storage stable and thus ready-to-use composition.

3.4.3 Furthermore, none of the remaining cited documents suggests an aqueous formulation of AMG 416 having a pH between 2.0 and 5.0 to solve the problem posed.

3.4.4 In this context the appellant argued that formulation of a peptide in aqueous solution is usually preferred since it is the easiest one and that, only if it proved not satisfactorily, then a lyophilisation would be considered (see D2, page 146, first full paragraph, D7, page 243, left column, second full paragraph, D8, page

S22, right column under "Recommendations" and D19, page 102 section "liquid formulation").

One of the first tests in early stages of formulation development of aqueous solutions would be the determination of the optimum pH (see D3, page 191, left and right columns, p192, left column, page 764, Figure 26-6; D5, page 502, 4.7.1, page 504, Figure 4.12; D2, page 147, 8.2; D7, page 240, right column, above table 9.5; D8, page S22, Section "C. pH"; D19, page 95, second paragraph).

According to the appellant, the skilled person would thus have arrived at the present pH range by carrying out routine pH stability studies. In this context, the appellant referred to the Case Law of the Boards of Appeal, 9th Edition, 2019, I.D.9.19.6 in which it is stated that "enhanced effects cannot be adduced as evidence of inventive step if they emerged from obvious tests".

3.4.5 This argument is not convincing. In the Board's view, the disclosures of the documents cited by the appellant do not establish that the standard formulation development for peptides would necessarily be to first study the formulation in aqueous solution, and then, only if this would not be successful, consider lyophilisation. On the contrary, when considering the overall teaching of the cited documents and not merely the passages cited by the appellant, the skilled person would not have had any reasonable expectation of success of formulating AMG 416 as an aqueous solution.

In view of D2, D8 and D19, the formulation of a peptide in solution, let alone in aqueous solution, does indeed not appear to be necessarily the first option nor to be

very successful (see for example D2 page 146, first full paragraph "approximately 200 peptides and proteins are being studied in the clinic, most of which are freeze-dried products"; D8, page S22, right column, second paragraph, "lacking long term stability data and having to rely on untrustworthy stability predictions from stressed samples, undertaking the development of a solution form can be risky"; D19, paragraph bridging pages 10-11, "as many biopharmaceuticals are not sufficiently stable to achieve a 2-year expiry in a liquid state, more than 50% of currently marketed biopharmaceuticals are introduced as lyophilized formulations. [...] the enhanced stability of lyophilized drugs often avoids the emergence of stability issues during later stages of development").

Moreover the documents D3, D5 and D7 cited by the appellant do not specifically relate to peptides and also discuss other formulations including solid state formulations and suspensions. A prioritisation of the formulation of peptides as solutions cannot therefore be derived from these documents.

Finally not only aqueous solutions but also non-aqueous solutions and emulsions constitute alternatives when willing to prepare ready-to-use compositions (see for example D1, paragraphs [085], D6 page 8, right column, second paragraph, first sentence and D8, page S23).

The skilled person would therefore not have been particularly motivated to prepare an aqueous solution. Performing pH stability studies would thus not have been obvious, in particular as pH is not the only parameter influencing storage stability (see for example D3, page 190, right column 2 last paragraphs

and page 191, first paragraph below "Solution Stability"; D7, page 240, right column).

The present situation is thus different from the one discussed in the passage of the Case Law of the Boards of Appeal cited by the appellant.

3.4.6 The appellant further brought forward that AMG 416 would not contain most of the amino acids which are known to lead to stability issues in peptides (see D2, pages 149, 150 and 153; D8 pages S4, A., S5 and S6). According to the appellant, the only expected degradation reactions for AMG 416 would involve the hydrolysis of the amide function at the C-terminal at very low pH and the disulfide exchange at higher pH, the second reaction being the main one (see D8, page S22). Thus the skilled person would expect AMG 416 to be stable at acidic pH, although not at very low pH. Contrary to the assertion made in the patent in suit (see paragraph [0005]), peptides with a disulfide bridge could be stabilised at acidic pH (see D8, page S22, left column, in chapter C. pH). This knowledge would constitute a further motivation for the skilled person to formulate AMG 416 as an aqueous solution at acidic pH.

3.4.7 The Board does not agree with this conclusion. Documents D2 and D8 generally teach that some amino acids may have a destabilising effect on a peptide. However, the Board observes that the absence of these amino acids in AMG 416 does not guarantee that this specific peptide would indeed be stable at low pH. As stressed by the respondent, stability of a peptide cannot be entirely predicted merely from its sequence (see D19, page 94, first sub-paragraph under "Lyophilization Design [...]", third sentence). In the

absence of specific information regarding AMG 416, it would have been considered to be prone at least to some extent to the same stability issues as any other peptide. Furthermore there is no unambiguous teaching regarding the boundary between the "very low pH" at which hydrolysis would be expected and the "low pH" at which the disulfide exchange would not occur, so that the skilled person would have had concerns regarding the stability of AMG 416 at "low pH".

3.4.8 Finally the appellant cited decision T 1214/17. According to the appellant, this decision was highly relevant to the present case as the underlying case also related to provision of a solution of an active ingredient in a specific pH range. The distinguishing feature was also the pH range and it led to a stable product, avoiding hydrolysis and epimerisation reactions. In this decision the board concluded that the claimed subject-matter was not inventive in view of common general knowledge which suggested to carry out routine stability studies to establish a pH profile of an active ingredient. The same conclusion would apply in the present case since the skilled person would be able to identify which degradation reactions may occur and would thus be motivated to address them.

3.4.9 In the Board's view the case underlying T 1214/17 differs in several aspects from the present case.

In the case underlying T 1214/17, the closest prior art document already generally disclosed ready-to-use buffered aqueous solutions of the active ingredient. Furthermore, the active ingredient was a small molecule for which structure related specific degradation reactions (epimerisation and hydrolysis) and expected degradation products could be identified. The objective

technical problem was accordingly formulated to address stability against these two specific reactions. These structure related degradation reactions were furthermore known from common general knowledge (supported by the prior art) to be pH dependent. The skilled person found therefore a motivation to perform specifically pH-stability studies to solve the problem posed, *i.e.* avoiding specific degradation reactions. Furthermore the closest prior art document itself referred to acetates as suitable buffers and a structurally related compound had been shown to be stable against epimerisation at a pH in the claimed range. This provided additional pointers towards the claimed pH range.

In the present case, the distinguishing feature is not merely the pH range but also the provision of an aqueous solution. The skilled person would therefore first have had to contemplate providing AMG 416 in the form of an aqueous solution, before even studying the pH thereof. Moreover, the active ingredient is a peptide, which is generally known to pose more complex stability issues when formulated in solution. Merely general considerations regarding possible degradation reactions (deamidation and dimerisation) were made but there was at the priority date no specifically identified degradation product for AMG 416. For the reasons already detailed above (see 3.4.1 to 3.4.5), the Board considers that the provision of an aqueous solution of AMG 416 would not have appeared obvious to the skilled person when aiming at a storage stable formulation. Furthermore, contrary to the case underlying T 1214/17, there was no motivation to give priority to pH-stability studies over the study of any other parameter possibly influencing the stability of the peptide in solution. Finally, in the present case,

the prior art does not provide any particular pointer towards the claimed pH range.

The conclusions reached in T 1214/17 do therefore not apply to the present case.

3.5 As a result the subject-matter of granted claim 1 involves an inventive step. The same reasoning applies *mutatis mutandis* to granted claims 2-15.

3.6 Accordingly, the ground of appeal according to Article 100(a) EPC in combination with Article 56 EPC does not prejudice the maintenance of the patent as granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated