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**Datasheet for the decision
of 11 July 2019**

Case Number: T 1147/16 - 3.3.07
Application Number: 06737947.9
Publication Number: 1858488
IPC: A61K9/19, A61K47/26, A61K47/02,
A61K47/12, A61K31/65, A61K9/08
Language of the proceedings: EN

Title of invention:

TIGECYCLINE COMPOSITIONS AND METHODS OF PREPARATION

Patent Proprietor:

Wyeth LLC

Opponents:

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Rechtsanwälte PartG mbB & Dr. Michael Eder
Taylor Wessing LLP
Hollatz, Christian
PENTAFARMA S.A.

Headword:

Tigecycline Compositions / WYETH

Relevant legal provisions:

EPC Art. 123(3), 56, 100(a), 100(b), 123(2), 84
EPC R. 80

Keyword:

Amendments - broadening of claim, main request, auxiliary requests 1-3 (yes)

Inventive step - auxiliary requests 4-8 (no) - auxiliary request 9 (yes)

Decisions cited:

T 0227/89



Beschwerdekammern

Boards of Appeal

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Case Number: T 1147/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 July 2019

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
15 March 2016 concerning maintenance of the
European Patent No. 1858488 in amended form.**

Composition of the Board:

Chairman D. Boulois
Members: E. Duval
P. Schmitz

Summary of Facts and Submissions

I. European patent number 1 858 488 was granted on the basis of 17 claims. Independent claim 1 read as follows:

"1. A composition comprising:
(a) tigecycline;
(b) a carbohydrate chosen from lactose, mannose, sucrose and glucose; and
(c) an acid or buffer
wherein the pH of the composition is between 3.0 and 7.0."

Dependent claim 3 related to:

"3. The composition according to anyone of claims 1 to 2 wherein the composition is lyophilized."

II. Four oppositions were filed against the patent in suit (hereinafter "the patent") on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed.

Opponent 2 subsequently withdrew its opposition in the course of the opposition proceedings.

III. The opposition division took the interlocutory decision that, on the basis of auxiliary request 4, the patent met the requirements of the EPC.

IV. The decision was based on a main request and auxiliary requests 1-4 filed by letter dated 4 January 2016.

Claims 1, 7 and 15 of the **main request** read as follows:

"1. A composition which is an aqueous solution comprising:

- (a) tigecycline;
- (b) a carbohydrate chosen from lactose, mannose, sucrose and glucose; and
- (c) an acid or buffer

wherein the pH of the composition is between 3.0 and 7.0."

"7. A process for preparing a tigecycline composition comprising combining one of the following carbohydrates: lactose, mannose, sucrose, or glucose, for reducing epimerization with tigecycline and water to form a solution; reducing the pH of the solution to between 3.0 and 7.0 with an acid or buffer to reduce oxidative degradation; and lyophilizing the solution to dryness."

"15. A lyophilised composition obtainable by the process of anyone of claims 7 to 8 or 10 to 13."

Auxiliary requests 1-3 also each contained a claim directed to a lyophilised composition obtainable by said process, wherein in the process claim the carbohydrate was limited to lactose and / or the acid or buffer were limited to 1.0 N HCl or gentisic acid.

Auxiliary request 4 contained no claim directed to a lyophilised composition obtainable by said process. Claim 1 of auxiliary request 4 was identical to claim 1 of the main request.

- V. As far as relevant to the present decision, the decision under appeal can be summarised as follows:
- (a) The main request did not comply with the requirements of Article 123(3) EPC: claim 3 of the patent as granted was limited to lyophilised compositions comprising an acid and having a pH between 3.0 and 7.0, whereas in claim 15 of the main request the composition resulted from the lyophilisation of such a solution but did not necessarily retain the acid or a pH in this range after lyophilisation.
 - (b) The same deficiency under Article 123(3) EPC applied to auxiliary requests 1-3.
 - (c) Auxiliary request 4 complied with the requirements of Article 123(2) and 84 EPC. Its subject-matter was novel over D14 and was sufficiently disclosed. With regard to inventive step, D1, D15 and D45 were considered as equally good springboards. The differentiating features, in particular the addition of a carbohydrate, led to an enhanced stability of the lyophilised tigecycline compositions against both oxidation and epimerisation. The problem to be solved was the provision of aqueous compositions which upon lyophilisation possessed enhanced stability against both oxidation and epimerisation, compared to other lyophilised tigecycline products. The use of the claimed carbohydrates to reduce epimerisation in compounds that resemble tigecycline was not suggested in the prior art. Hence auxiliary request 4 also complied with the requirements of Article 56 EPC.

VI. In the present decision, reference is made to the following documents:

D1: Garrison et. al., Clinical Therapeutics, 27(1) (2005), 12-22

D2: CN 1390550A

D2a: translation of CN 1 390550A

D7: Zacharis et al., Proc. Natl. Acad. Sci. USA, 96 (1999), 1201-1205

D8: Nagggar et al., Pharmazie, 29(2) (1974), 126-129

D10: Bedu-Addo, Pharmaceutical Technology, (2004), 10-18

D11: Curtis et al., British Medical Journal, (1977), 242-244

D12: WO 2005/004874 A1

D12a: EP 1 645 277 A1, EP regional counterpart application of D12, in English

D15: US 5,675,030

D19: Fakes et al., Moisture sorption behavior of selected bulking agents used in lyophilized products, PDA J Pharm Sci Technol. 2000, 54(2), 144-149

D20: Herman et al., The effect of bulking agent on the solid-state stability of freeze-dried methylprednisolone sodium succinate , Pharmaceutical Research 1994, 11, 1467

D24: US 2005/0020610

D37: Declaration of Dr Robert Williams, University of Texas

D45: Original Tygacil® Label

D49: WO 2014/191552

D50: Podhorniak et al., Journal of Food Protection, Vol. 62, No. 5, 1999, Pages 547 548

D51: 2nd declaration of Christian L. Ofslager

Annex 1: Experimental Protocol filed by the appellants-opponents 1 with their statement of grounds of appeal

D54: Declaration of Nerija Melninkaitis and experimental protocol (filed by the appellant-patent proprietor by letter dated 9 March 2017)

VII. The patent proprietor, opponents 1 and opponent 4 each filed an appeal against the interlocutory decision of the opposition division.

VIII. By letter dated 1 December 2016, the appellant-patent proprietor defended its case on the basis of the main request and auxiliary requests 1-6 filed before the opposition division, and auxiliary requests 7 and 8 filed with this letter.

Claim 1 of **Auxiliary request 5** was identical to claim 1 of the main request.

Claim 1 of **Auxiliary request 6** was identical to process claim 7 of the main request.

Claim 1 of each of **auxiliary requests 7 and 8** read as follows:

"1. A composition which is an aqueous solution comprising:

(a) tigecycline;

(b) a carbohydrate chosen from lactose, mannose, sucrose and glucose; and

(c) HCl

wherein the pH of the composition is between 3.0 and 7.0."

IX. In a communication pursuant to Article 15(1) RPBA dated 24 May 2019, the Board *inter alia* expressed doubts regarding the achievement of an improved stability against epimerisation for mannose and glucose.

- X. By letter dated 10 June 2019, the appellant-patent proprietor filed auxiliary requests 9 and 10.

Claims 1 and 6 of **auxiliary request 9** read as follows:

"1. A composition which is an aqueous solution comprising:

- (a) tigecycline;
- (b) lactose; and
- (c) an acid or buffer

wherein the pH of the composition is between 3.0 and 7.0."

"6. A process for preparing a tigecycline composition comprising combining lactose, for reducing epimerization with tigecycline and water to form a solution; reducing the pH of the solution to between 3.0 and 7.0 with an acid or buffer to reduce oxidative degradation; and lyophilizing the solution to dryness."

- XI. Oral proceedings took place on 11 July 2019 in the presence of the appellant-patent proprietor. Each of the appellants-opponents 1, the appellant-opponent 4 and the respondent-opponent 3 had announced its absence by earlier letter.

- XII. The arguments of the appellant-patent proprietor can be summarised as follows:

- (a) Claim 15 of the main request did not extend the protection conferred by the patent. The relevant claims of the patent as granted were claims 1 and 3. Since it was not possible to measure the pH of a solid, the pH feature of claim 1 required interpretation, either by ignoring this feature, or

based on the understanding that the protonation state of tigecycline in solution would be remembered in the lyophilised state. The pH of reconstituted solutions was in that respect not relevant. Both claims 1 and 3 as granted and claims 7 and 15 of the main request involved the same process of lyophilisation of an aqueous solution of tigecycline containing an acid or buffer, such that the fate of the acid or buffer would be the same. Thus the main request complied with the requirements of Article 123(3) EPC.

- (b) Claim 1 of auxiliary request 4 found basis, in the sense of Article 123(2) EPC, in the application as filed in claims 1 and 2, as well as page 6, 2nd paragraph; page 7, 2nd paragraph; page 8, 2nd, 4th and 5th paragraphs; page 9, 2nd paragraph. In this respect, whether or not claim 1 also covered aqueous tigecycline solutions made by reconstituting lyophilised solid was irrelevant, because claim 1 did not individualise such an alternative embodiment.
- (c) Claim 1 of auxiliary request 4 neither lacked clarity nor sufficiency of disclosure. The skilled person would have no difficulty in measuring the pH of an aqueous solution, reconstituted or otherwise.
- (d) The closest prior art was represented by D15, rather than D1, D45 or D2. D15 disclosed an aqueous solution of tigecycline at a pH of 6.5. The distinguishing technical feature of claim 1 was the presence of a carbohydrate selected from lactose, mannose, sucrose and glucose. The resulting technical effect was a good tigecycline stability with respect to epimerisation while maintaining

good stability against oxidation, as shown by the experimental data in the patent. The technical problem was the provision of tigecycline compositions, both aqueous and lyophilised, with good stability against both oxidation and epimerisation. The claimed solution was not suggested in D15 or in any other prior art.

XIII. The arguments of the appellants-opponents can be summarised as follows:

- (a) Claim 15 of the main request violated Article 123(3) EPC. A composition obtainable by the process of adjusting the pH to between 3.0 and 7.0 prior to lyophilisation would no longer necessarily contain an acid in view of the possibility that volatile acids would be completely removed from the composition upon lyophilisation. Furthermore the product-by-process claim 15 was not limited by the feature of a pH between 3.0 and 7.0, because the pH may change upon lyophilisation due to removal of a volatile acid. Any lack of clarity in respect of the pH feature could not be used in favor of the appellant-patent proprietor.
- (b) In auxiliary request 4, the deletion of former claims 4 and 5 did not address any ground for opposition, in contravention to Rule 80 EPC, and raised doubts as to the interpretation of claim 1, contrary to Article 84 EPC.
- (c) The aqueous compositions of claim 1 of auxiliary request 4 encompassed reconstituted solutions. However, the description as filed disclosed the claimed pH feature only in the context of an aqueous solution prior to lyophilisation. No basis

could be found in the application as filed for a claim covering a reconstituted aqueous solution comprising tigecycline, a carbohydrate, an acid or buffer and having a pH between 3 and 7. Thus claim 1 did not fulfill the requirements of Article 123(2) EPC.

- (d) The boundaries of product claim 1 of auxiliary request 4, covering reconstituted solutions, were so unclear that this deficiency also led to a lack of sufficiency of disclosure. Starting from a lyophilised composition made from an aqueous tigecycline solution at pH 3.0 to 7.0, a reconstituted solution could have different pH depending on the volume for reconstitution. This reconstitution volume was a relevant parameter for the pH measurement which was undefined, as a result of which any claim covering reconstituted solutions contravened the requirements of Article 100(b) EPC.
- (e) D15 represented a more reasonable starting point for the assessment of inventive step than D1 or D45. D15 disclosed a tigecycline solution at a pH of 6.5. The skilled person seeking to improve the stabilisation against epimerisation would be prompted to add lactose or glucose in view of D2. Alternatively, the claimed subject-matter was obvious over a combination of D15 with D11, D12/ D24, D8, D10, D50, D19 or D20.

Additionally, no improvement in stability had been demonstrated over the breadth of the claims: no tests had been provided for aqueous compositions prior to lyophilisation, or for acids/buffers other than hydrochloric acid or gentisic acid, or for different ratios of tigecycline to carbohydrate, or

for a pH of 7.0. On the contrary, D49 and Annex 1 showed that lactose could not prevent epimerisation in the lyophilised state for compositions whose pH was adjusted with certain acids.

The claimed aqueous compositions, covering reconstituted solutions, could also not benefit from an effect achieved only in the lyophilised compositions, and resulted from an obvious step of reconstituting the tigecycline composition of D15 with a dextrose solution, which was a common diluent.

Even if an effect of the selected carbohydrate on the prevention of epimerisation was taken into account, this additional effect was at best to be considered a bonus effect which could not justify the presence of an inventive step. The finding that certain additives were capable of preventing epimerisation was part of the more general problem of preventing any tigecycline degradation. Lactose as a common bulking agent was an obvious excipient to be added in view of its known stabilising properties.

D2 also represented a reasonable starting point for the assessment of inventive step. D2 disclosed the addition of lactose or glucose to an analogue of tigecycline, namely minocycline. In view of the disclosure of D2, the features of claim 1 of auxiliary request 4 were known with the exception of tigecycline. The skilled person however knew from D1 that minocycline and tigecycline were analogues.

- XIV. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained according to:
- the main request underlying the decision under appeal, or alternatively
 - one of auxiliary requests 1-6 filed before the opposition division, or
 - auxiliary requests 7 or 8 filed by letter dated 1 December 2016, or
 - auxiliary requests 9 or 10 filed by letter dated 10 June 2019.
- XV. Both the appellants-opponents 1 and the appellant-opponent 4 requested that the decision under appeal be set aside and the patent be revoked.

The respondent-opponent 3 made no request during the appeal proceedings.

Reasons for the Decision

Absence of the appellants-opponents 1 and 4 and the respondent-opponent 3

1. None of the appellants-opponents 1, the appellant-opponent 4 or the respondent-opponent 3 attended the oral proceedings.

In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the oral proceedings were held without these parties. By their decision not to attend the oral proceedings, the appellants- and respondent- opponents have chosen not to make any further submissions during

such proceedings. These duly summoned parties have to be treated as relying only on its written case.

Main request, claim 15

2. Article 123(3) EPC

In the main request, as compared with the patent as granted, a new independent claim 15 is introduced which pertains to lyophilised compositions defined in terms of the process for their preparation. The question arises whether the protection conferred by the patent is thereby extended.

Pursuant to Article 123(3) EPC, the European patent may not be amended in such a way as to extend the protection it confers. Compliance with this criteria is assessed by comparing the protection conferred by the totality of the claims before amendment, i.e. as granted, with that of the claims after amendment.

2.1 Scope of the patent as granted

The claimed compositions in the patent as granted (see claims 1 and 3 of the patent reproduced above in I.) are *inter alia* limited by the following features:

- the [lyophilised] composition comprises an acid or buffer, and
- the pH of the composition is between 3.0 and 7.0.

All parties agreed that the feature pertaining to a pH of 3.0-7.0 is unclear in the context of lyophilised compositions, since a pH cannot be measured in solids. The claims of the patent thus require interpretation.

- 2.1.1 According to the appellant-patent proprietor's first proposed alternative interpretation, the pH feature of claim 1 is simply ignored in the context of solid compositions. The Board cannot accept this interpretation: contrary to the appellant-patent proprietor's assertion, the description does mention a pH of 3.0-7.0 in the context of solids (see [0021]) or lyophilised powders (see [0023]). Thus, the pH feature is a limiting feature of claim 1 and should be given a meaning in light of the patent specification. There is no basis for interpreting the claim without this limitation.
- 2.1.2 An alternative interpretation, adopted in the decision under appeal, is that the pH feature of claim 1 of the patent as granted refers to the pH of a (reconstituted) solution after addition of water. Following another interpretation, proposed by the appellant-patent proprietor, the protonation state of tigecycline in aqueous solution would be remembered in the lyophilised state such that, on aqueous reconstitution, a solution with essentially the same pH as that prior to lyophilisation would be obtained.
- 2.1.3 In the Board's opinion, neither interpretation is fully satisfactory, in the sense that the pH feature remains ambiguous in both cases: the patent neither teaches how this protonation state should be assessed, nor does it describe a method for adding water to the lyophilised composition so as to measure its pH.

Nonetheless, considering that the patent is silent about the appellant-patent proprietor's alleged pH memory mechanism, and since claims 1 and 3 define the pH range of 3.0-7.0 in respect of the [whole] composition or solid lyophilisate (i.e. including

carbohydrate and acid or buffer), the Board sees no basis for interpreting the pH feature of the granted claims, as proposed by the appellant-patent proprietor, as merely referring to the protonation state of tigecycline.

For the purposes of Article 123(3) EPC, it must be convincingly shown that the claimed subject-matter is still limited, after amendment, to formulations characterised by this unclear pH feature. The above difficulties in resolving the ambiguity of this feature cannot justify, to the appellant-patent proprietor's benefit, a broader interpretation in the absence of basis therefor in the patent specification.

The feature of claim 1 relating to the pH of the lyophilised composition is thus interpreted as referring to the pH of a (reconstituted) solution after addition of water.

2.2 Scope of claim 15 of the main request

- ### 2.2.1 Claim 15, introduced in the main request, pertains to lyophilised compositions defined in terms of the process for their preparation, namely to those obtainable by a process comprising
- combining the carbohydrate with tigecycline and water to form a solution;
 - reducing the pH of the solution to between 3.0 and 7.0 with an acid or buffer; and
 - lyophilizing the solution to dryness.

Accordingly, it must be assessed whether a composition whose pH has been reduced to between 3.0 and 7.0 with an acid or buffer is still necessarily characterised,

after lyophilisation, by the presence of an acid or buffer and by a pH between 3.0 and 7.0.

For the following reasons, the Board finds that this is not the case.

- 2.2.2 Firstly, a complete removal of the acid or buffer during lyophilisation cannot be ruled out. As acknowledged by the appellant-patent proprietor (statement of grounds of appeal, point 2.6.2), the fate of the acid or buffer in the lyophilisation process will depend on the acid or buffer in question and the precise lyophilisation conditions employed. Yet neither the acid or buffer nor the lyophilisation conditions are in any way limited in claim 15.

The possible influence of lyophilisation on acid or buffer content is confirmed by D7 (cf. abstract), which shows that buffer ions may in some cases be completely removed during lyophilisation. The appellant-patent proprietor did not provide any compelling reasons why this phenomenon observed for subtilisin in the low-water conditions of D7 would fail to arise in any of the broadly defined conditions of claim 15. The Board accepts the argument of the appellant-patent proprietor, according to which tigecycline is more basic than the subtilisin studied in D7, because its structure comprises two amine moieties. Nonetheless, tigecycline remains a weak amine base.

Accordingly, claim 15 covers compositions prepared from solutions comprising a volatile acid or buffer, or lyophilised under conditions such that the acid or buffer evaporated and disappeared, as pointed out in the decision under appeal (point 6.7): the compositions

of claim 15 do not necessarily comprise an acid or buffer as required by claim 1 as granted.

- 2.2.3 The pH feature of claim 1 as granted is also not necessarily met by the lyophilised compositions of claim 15 of the main request.

Claim 15 allows for the lyophilisate to be prepared from an aqueous composition having a pH of 7.0. In such a case, even a partial loss of the acid or buffer component during lyophilisation may modify the composition and bring its corresponding pH upon reconstitution to a value beyond the upper limit of 7.0.

The appellant - patent proprietor cited D51 as evidence that the pH before lyophilisation and after reconstitution are essentially the same (see D51, paragraph 8). However, the Board concurs with the opposition division's finding that the experiments described in D51 are conducted in specific conditions involving only HCl as acid, and that small variations in pH are nonetheless observed. Thus D51 does not demonstrate that the pH before lyophilisation and after reconstitution are necessarily identical.

Likewise, the low levels of oxidative degradation observed for the lyophilised compositions of the patent or in D54 do not rule out a partial loss of acid or buffer component, leading to a composition of the lyophilised solid corresponding to a pH falling outside the range 3.0-7.0: despite the role of an acidic pH mentioned in the patent in minimising oxidation, no quantitative correlation between oxidation level and pH value is given.

2.2.4 In conclusion, the criteria of Article 123(3) EPC are not fulfilled by claim 15 of the main request.

Auxiliary requests 1-3

3. Article 123(3) EPC

3.1 Claim 13 of auxiliary request 1 relates to a lyophilised composition obtainable by the process of claim 6, in which the carbohydrate is limited to lactose. This limitation is immaterial to the issues identified above in relation with the presence of the acid or buffer and the pH range. Therefore, auxiliary request 1 does not meet the requirements of Article 123(3) EPC for the same reasons as the main request.

3.2 In claims 11 and 9 of auxiliary requests 2 and 3, respectively, the acid or buffer used before lyophilisation is selected from HCl or gentisic acid. The appellant-patent proprietor expressed the view that HCl is a strong acid forming a tigecycline salt leading to a pH memory effect, and that gentisic acid is unlikely to evaporate owing to its high melting temperature. However, it is not a feature of claims 11 and 9 that all the acid or buffer present in the composition be bound to tigecycline as a salt. Furthermore, the lyophilisation conditions remain likewise undefined in both auxiliary requests 2 and 3. As reasoned above, even a partial loss of acid is liable to bring the pH from 7.0 to just beyond 7.0. In this circumstances, the lack of convincing evidence that no change in the amount of said acids or in the pH value can occur during lyophilisation, irrespective of the conditions in which it is carried out, lead to the conclusion that the requirements of Article 123(3) EPC are still not met.

Auxiliary request 4 - claim 1

4. Inventive step

4.1 According to the patent (see [0001]), the objective of the invention is to provide tigecycline compositions having improved stability in both solid and solution states. The claimed invention seeks to address this problem by formulating the tigecycline in an aqueous solution comprising an acid or buffer and a carbohydrate chosen from lactose, mannose, sucrose and glucose, and having a pH between 3.0 and 7.0 (as defined in claim 1). According to the patent (see [0019]), the acidic pH minimizes oxidative degradation, whereas the carbohydrate stabilizes tigecycline against epimer formation at acidic pHs.

4.2 D15 mentions the problems of degradation of tigecycline by epimer formation and oxidation (see column 1), and discloses (see example 9) an aqueous composition comprising tigecycline and hydrochloric acid, having a pH of 6.5, and the lyophilisation of this composition. The Board considers D15 to represent a suitable starting point for the assessment of inventive step.

All parties agreed that D15 is a more reasonable starting point for the discussion of inventive step than D1 or D45. The Board concurs.

D2 is concerned with the provision of (aqueous solutions for the preparation of) freeze-dried compositions of minocycline, comprising in some alternatives a support agent such as glucose or lactose (see translation D2a, claims). However, D2 neither mentions tigecycline nor the problem of its

stabilisation. Consequently, the Board does not share the view of appellant-opponent 4 that D2 is suitable as closest prior art.

- 4.3 The claimed subject-matter differs from the aqueous solution of example 9 of D15 by the presence of a carbohydrate chosen from lactose, mannose, sucrose and glucose.
- 4.4 According to the appellant-patent proprietor, the effect of the carbohydrate is a reduction of the unwanted epimerisation that occurs at acidic pH.
- 4.4.1 Regarding the carbohydrates lactose and sucrose, stability / epimerisation data are reported in the patent for comparable lyophilised samples made from solutions adjusted to pH 4.5-7.0 with HCl or gentisic acid, and differing only in respect of the presence of the carbohydrate (examples and tables 1, 3, 4a and 4b of the patent). The data indeed suggest that the differentiating feature, namely the presence in the aqueous composition of a carbohydrate selected from lactose and sucrose, leads to a reduction of epimerisation in the resulting lyophilisate.

This effect credibly arises for various ratios of tigecycline to carbohydrate, as shown in example 6.

D54 supports that the stabilising effect of lactose is obtained across a wide range of acids, as shown, for each acid, by the amounts of epimer after 5 or 10 days at 40°C/75%RH for compositions differing only by the presence of lactose.

The Board does not consider D49 and Annex 1 as convincing counter-evidence regarding the effect of the

carbohydrate on stability of the resulting lyophilisate. Neither D49 (table 1) nor Annex 1 allow for a meaningful comparison between compositions differing only by the presence of the carbohydrate. Thus no conclusion can be drawn from D49 or Annex 1 as to the effect, or absence thereof, of the carbohydrate on epimerisation in the lyophilisate.

4.4.2 However, it has not been shown that this effect on epimerisation extends to glucose and mannose.

Table 4c of the patent reports epimerisation levels of 1.02-1.23% for a composition comprising glucose or mannose. In the same table 4c, higher epimerisation levels are shown for compositions comprising different carbohydrates (e.g. ribose, xylose). However, table 4c provides no directly comparable data for a composition differing only by the absence of carbohydrate, and produced and tested under the same conditions.

The appellant-patent proprietor attempted to derive an effect for glucose or mannose from indirect comparisons with table 4b. However, the data in table 4b, in particular the epimerisation level of 2.72% for a composition lacking any carbohydrate, is given for a composition prepared at a different temperature (-70°C vs -50°C) and a different pH (6.0 vs 5.0), and tested not only for a different amount of time (89 hours vs 42 days) but also in different temperature and humidity conditions (40°C vs 25°C/60%RH). In particular, the exposure of the samples to a lower temperature (25°C vs 40°C) may account in part for the lower epimerisation level, as confirmed by the declaration D37 (paragraph 40). As a result, no meaningful conclusion can be drawn from this indirect comparison.

- 4.4.3 In conclusion, the Board finds that the presence of lactose or sucrose in the aqueous composition is shown to lead to a reduction of epimerisation in the resulting lyophilisate, independently of the type of acid or ratio of tigecycline to carbohydrate. However, the same effect is not shown to extend to glucose and mannose.
- 4.5 As no effect is shown to arise over the whole scope of the claims, the problem to be solved is the provision of a further formulation of tygecycline.
- 4.6 Since glucose and lactose are known bulking agents (see e.g. D2/D2a, claim 5, or D10, page 12) to be added to compositions for lyophilisation, no inventive step can be acknowledged to the subject-matter of claim 1.

In conclusion, auxiliary request 4 does not meet the requirements of Article 56 EPC.

Auxiliary requests 5-8

5. Inventive step

Since claim 1 of each of the auxiliary requests 5-8 still covers the carbohydrates glucose and mannose, and since the amendments only concern features which are already disclosed in the closest prior art D15, the same conclusion applies: auxiliary requests 5-8 do not meet the requirements of Article 56 EPC

Auxiliary request 9 - claim 1

6. Article 123(3) EPC

As compared with the patent as granted, claim 1 of auxiliary request 9 is limited to aqueous solutions in which the carbohydrate is lactose. The requirements of Article 123(3) EPC are thus fulfilled.

7. Article 123(2) EPC

The opposition division reasoned that the subject-matter of claim 1 finds basis in the application as filed, namely in claims 1 and 2 in combination with the passages of the description disclosing the feature "aqueous solution" (see page 6, 2nd paragraph; page 8, 4th and 5th paragraphs; page 9, 2nd paragraph) and the feature pertaining to a pH of 3.0 to 7.0 (see page 6, last paragraph; page 8, 2nd paragraph; page 9, 2nd paragraph). The Board concurs.

Both the appellants-opponents 1 and appellant-opponent 4 base their objection of added subject-matter on the fact that claim 1 covers compositions obtained on reconstitution, whereas the application as filed only disclosed aqueous compositions having the stated pH in the context of solutions prior to lyophilisation.

The Board does not share this view. Claim 1 relates to an aqueous solution which is not characterised by its method of production or its later use, i.e. claim 1 does not recite as alternatives that the composition of claim 1 results from a reconstitution step or that it is destined to be lyophilised. The generally defined composition of claim 1 is derivable from the above-cited passages of the application as filed. It is for

that purpose not relevant that the application as filed states that these compositions are destined to be lyophilised, because this statement does not affect the definition of the solution.

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

8. Rule 80 EPC

The deletion, in auxiliary request 4, of dependent claims 4 and 5 (as compared with the claims as granted) does not contravene Rule 80 EPC, because such an amendment could be occasioned by e.g. the ground for opposition under Article 100(c) EPC, whether that ground has been invoked by an opponent or not.

The requirements of Rule 80 EPC are thus met.

9. Article 84 EPC

Contrary to the opinion of Appellant-opponent 4, the deletion of claims 4 and 5 does not cause claim 1 to lack clarity. The deletion of claims 4 and 5 is immaterial to the question of whether a lack of clarity exists in the wording of claim 1. It clearly follows from its wording that claim 1 covers aqueous compositions comprising tigecycline, the stated carbohydrate and acid/buffer, and having a pH of 3.0 to 7.0, whether they were prepared by reconstitution of a lyophilisate or otherwise.

Accordingly, the amendments do not introduce any non-compliance with Article 84 EPC.

10. Sufficiency of disclosure

According to the appellants-opponents 1, a person skilled in the art is not able to identify whether a reconstituted aqueous solution having a given pH is encompassed by the claims or not. The lack of information as to the correct volume for reconstitution of the solution means that the boundaries of claim 1 are so unclear that the criteria of sufficiency of disclosure are not fulfilled.

The Board does not consider that claim 1 lacks clarity. Claim 1 covers aqueous compositions comprising tigeicycline, the stated carbohydrate and acid/buffer, and having a pH of 3.0 to 7.0, whether they were prepared by reconstitution of a lyophilisate or otherwise. The patent sufficiently discloses how to prepare such compositions. The pH of the claimed aqueous solution can be measured without difficulty by the skilled person. It follows from the explicit wording of claim 1 that, if a lyophilisate is reconstituted with a diluent in a volume such that the pH falls outside the range 3.0-7.0, then this reconstituted solution does not fall within the scope of claim 1.

As no lack of clarity is apparent, the objection of insufficiency of disclosure based thereon is unconvincing.

11. Inventive step

11.1 In contrast with claim 1 of auxiliary request 4, the carbohydrate in claim 1 of auxiliary request 9 is limited to lactose. Starting from the closest prior art

D15 (see point 4.1 above), the claimed subject-matter differs by the presence of lactose.

- 11.2 As explained above (see point 4.4), the presence of lactose in the aqueous composition credibly leads to a reduction of epimerisation in the resulting lyophilisate, independently of the type of acid or buffer and the ratio of tigecycline to carbohydrate.
- 11.3 Accordingly, the problem to be solved is the provision of tygecycline formulations having improved stability against epimerisation upon lyophilisation. It follows from the above reasoning that this problem can be regarded as solved.
- 11.4 None of the cited documents teaches that the addition of lactose will improve the stability of the tigecycline formulations against epimerisation upon lyophilisation.

D2 (see claim 5, translation D2a) shows the use of lactose as lyophilised powder supporting agent in minocycline formulations, but does not mention any effect of lactose on epimerisation.

D11 (see page 243, right column) addresses stability issues arising from the use of citric acid as excipient in tetracycline preparations, by replacing this excipient with lactose. This disclosure merely shows that lactose does not have the same detrimental effects on stability as citric acid. As noted by the opposition division, the skilled person would not infer from D11 that lactose prevents epimerisation.

D12 and D24 discuss the use of lactose in the stabilisation of a different compound, namely

tetrodoxin. The mechanism proposed in D12 (see paragraph [0033] of the equivalent D12a) relies on the formation of hydrogen bonds peculiar to the specific interaction of tetrodoxin and lactose, and there is no teaching in D12 or D24 that such a mechanism could be extrapolated to the significantly different structure of tigecycline.

D8 (see page 127) discloses that certain solubilisers such as polysorbate reduce epimerisation in tetracyclines. There is no mention of lactose in D8 nor any suggestion that it might behave similarly to polysorbate.

D10 (see page 12) relates to the stabilisation of liposomes and proteins. The disclosure of a stabilising effect of lactose against some unspecified physical or chemical degradation of these unrelated biomolecules upon lyophilisation does not make the specific action of lactose against the epimerisation of tigecycline obvious.

D50 relates to the stability of tetracycline in raw milk. It is neither concerned with stability against epimerisation upon lyophilisation, nor does it mention any effect of lactose.

D19 and D20 are concerned with the effect of common bulking agents, among which lactose and mannitol, on moisture absorption and stabilisation of lyophilised molecules against hydrolysis. Neither D19 nor D20 teach that the presence of lactose in a tigecycline formulation would exhibit reduced epimerisation upon lyophilisation. Absent any teaching about the respective effects of water and lactose on epimerisation in the lyophilisate, the Board is unable

to follows the argument of the appellants-opponents 1, according to which the absorption of moisture and its replacement with the bulking agent would be expected by the skilled person to lower the drug's propensity to epimerise.

- 11.5 The appellants-opponents 1 regard the particular effect of reduction of epimerisation as a bonus effect, with the consequence that the known more general stabilisation effect of lactose on lyophilisates would render the claimed subject-matter obvious. The Board does not agree.

As stated in T 227/89, in determining which effect is crucial and which is merely accidental (the so-called "bonus effect"), a realistic approach has to be taken, considering the relative technical and practical importance of those effects in the circumstances of a given case.

It is not contested that lactose is one of many commonly known bulking agents that may optionally be used to physically stabilise lyophilisates. However, as submitted by the appellant-patent proprietor, there is no suggestion in the art that a bulking agent is needed for a tigecycline composition, let alone desired (see D37, paragraph 29). In contrast, the issue of tigecycline C-4 epimerisation appears crucial considering that the C-4 epimer lacks the anti-bacterial efficacy of tigecycline, and that the epimerisation rate of tigecycline is particularly fast (see paragraphs [0010] and [0012] of the patent).

Thus the known potential use of lactose to stabilise lyophilisates does not equate with the specific effect of lactose on tigecycline epimerisation disclosed in

the patent, nor does this known optional use justify that the crucial epimerisation problem be disregarded in the assessment of inventive step.

- 11.6 The appellants-opponents 1 also expressed the view that the claims cover reconstituted solutions which do not make use of the teaching of the patent, i.e. the effect of lactose against epimerisation in the lyophilised state is not relevant for a reconstituted solution which is not destined to be lyophilised.

The Board does not share this opinion. The claimed aqueous composition is generally suitable for lyophilisation. No demonstration was adduced that, if the claimed aqueous solution was prepared by reconstitution, it would fail to give rise to the stabilising effect upon further lyophilisation. Accordingly, the argument that the claimed aqueous solution resulted from an obvious step of reconstituting the tigecycline composition of D15 with a dextrose solution is unconvincing, because it disregards the effect on epimerisation brought about by the claimed invention.

Consequently, the subject-matter of claim 1 of auxiliary request 9 involves an inventive step.

12. In process claim 6 of auxiliary request 9, the carbohydrate is likewise limited to lactose, such that the above conclusions also apply to its subject-matter. Lastly, auxiliary request 9 does not comprise any claim directed to lyophilised compositions defined in terms of the process for their preparation, and thus does not extend the protection conferred by the patent.

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 set of claims of auxiliary request 9 and a description adapted thereto.

The Registrar:

The Chairman:



B. Atienza Vivancos

D. Boulois

Decision electronically authenticated