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Case Number: T 0219/18 - 3.3.02

Application Number: 10707694.5

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Language of the proceedings: EN

Title of invention:
PROCESS FOR PURIFYING LIPOPEPTIDES

Patent Proprietor:
Xellia Pharmaceuticals ApS

Opponents:
Uexküll & Stolberg
Partnerschaft von Patent- und Rechtsanwälten mbB
Swindell & Pearson Limited

Headword:
DAPTOMYCIN PURIFICATION / XELLIA

Relevant legal provisions:
EPC Art. 84, 83, 54, 56

Keyword:
Clarity - (yes)
Sufficiency of disclosure - (yes)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 0219/18 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 26 January 2021

Appellant: (Opponent 2)	Swindell & Pearson Limited 48 Friar Gate Derby Derbyshire DE1 1GY (GB)
Representative:	FR Kelly 27 Clyde Road Ballsbridge, D04 F838 Dublin (IE)
Respondent: (Patent Proprietor)	Xellia Pharmaceuticals ApS Dalslandsgade 11 2300 Copenhagen S (DK)
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Party as of right: (Opponent 1)	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstrasse 4 22607 Hamburg (DE)
Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 19 October 2017 concerning maintenance of the European Patent No. 2398817 in amended form.**

Composition of the Board:

Chairman	M. O. Müller
Members:	M. Maremonti
	R. Romandini

Summary of Facts and Submissions

I. The appeal by opponent 2 (hereinafter "appellant") lies from the interlocutory decision of the opposition division, according to which European patent No. 2 398 817 (hereinafter "the patent") in its form modified on the basis of the then pending main request and the invention to which it relates meets the requirements of the EPC.

II. The main request found allowable by the opposition division contains 11 claims. Independent claims 1 and 7 read as follows:

"*1. A process for purifying daptomycin comprising the steps of*

(a) *loading a solution comprising partly purified daptomycin onto an anion exchange chromatography column;*

(b) *loading the solution of step a) onto a reverse phase chromatography column;*

(c) *loading the solution of step b) onto yet a reverse phase chromatography column at least once;*

wherein the elution buffer in a) is a monovalent salt solution; the elution buffer in b) and c) is aqueous alcohol; the first reverse phase chromatography column is eluted at pH 6.5-8.5; and the second reverse phase chromatography column is eluted at pH 2.5-3.5."

"*7. A process for purifying daptomycin containing the steps of*

(a) *subjecting a fermentation broth comprising daptomycin to one or several clarification steps;*

(b) *loading the solution of step a) onto an anion exchange chromatography column;*

(c) *loading the solution of step b) onto a reverse phase chromatography column;*

(d) *loading the solution of step c) onto yet a reverse phase chromatography column at least once;*

(e) *subjecting the resulting solution of step d) to one or several filtration steps;*

(f) *subjecting the filtrate of d) for lyophilisation; resulting in a purified powder of daptomycin;*

wherein the elution buffer in step c) and in step d) is aqueous alcohol; the first reverse phase chromatography column is eluted at pH 6.5-8.5; and the second reverse phase chromatography column is eluted at pH 2.5-3.5."

III. The following documents were among those cited during the opposition proceedings:

F1: US 6,696,412 B1

F2: US 4,874,843

F3: WO 96/32407 A1

F4: US 4,667,016

F6: US 4,537,717

F7: Mahoney and Hermodson, The Journal of Biological Chemistry, 1980, 255 (23), pages 11199 to 11203

F8: Bergström and Sjövall, ACTA Chemica Scandinavica, 1960, 14, pages 1693 to 1700

F9: Snyder, Dolan and Gant, Journal of Chromatography, 1979, 165, pages 3 to 30

F10: Dolan, Gant and Snyder, Journal of Chromatography, 1979, 165, pages 31 to 58

F11: Howard and Martin, Biochemical Journal, 1950, 46, (5), pages 532 to 538

IV. The opposition division came to, *inter alia*, the following conclusions on the claims of the main request:

- The claimed subject-matter fulfilled the requirements of Article 83 EPC.
- The subject-matter of claims 1 and 7 was novel over the disclosure of F1 and involved an inventive step in view of F1 taken as the closest prior art.

V. In the statement of grounds of appeal, the appellant contested the reasoning of the opposition division and raised objections under Articles 84, 83, 54 and 56 EPC. It also contested the validity of the priority claim.

In the context of inventive step, the appellant referred, *inter alia*, to

D10: Experiments 1 and 2 filed by the patentee by letter dated 2 September 2016.

VI. In its reply to the statement of grounds of appeal, the patentee (hereinafter "respondent") rebutted the arguments of the appellant. As regards inventive step, the respondent relied on the above-mentioned D10 and further corroborated its arguments with a newly filed experimental report A001.

VII. The parties were summoned to oral proceedings in accordance with their requests.

VIII. In preparation for the oral proceedings, the board issued a communication pursuant to Article 15(1) RPBA 2020 in which it expressed, *inter alia*, the preliminary opinion that the claimed subject-matter was clear, was sufficiently disclosed in the patent, was novel and involved an inventive step.

IX. By letter dated 5 October 2020, the respondent requested that the oral proceedings be held by videoconference.

X. By letter dated 30 October 2020, opponent 1, party to the appeal proceedings as of right within the meaning of Article 107, second sentence, EPC, announced that it would not be represented at the scheduled oral proceedings.

XI. By letter dated 16 November 2020, the appellant agreed to the oral proceedings being held by videoconference.

XII. By communication dated 20 November 2020, the board informed that the oral proceedings would be held by videoconference as agreed by the appellant and the respondent.

XIII. By letter dated 22 December 2020, the respondent submitted additional arguments and filed a set of claims and description pages according to an auxiliary request.

XIV. Oral proceedings before the board were held on 26 January 2021 by videoconference in the absence of opponent 1 pursuant to Rule 115(2) EPC and Article 15(3) RPBA 2020.

XV. Final requests

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

The respondent requests that the appeal be dismissed, meaning that the patent be maintained on the basis of the claims of the main request found allowable by the opposition division.

Alternatively, it requests that the patent be maintained in amended form on the basis of the claims and description pages according to the auxiliary request filed by letter dated 22 December 2020.

Opponent 1, party to these appeal proceedings as of right within the meaning of Article 107, second sentence, EPC, has not made any comment nor filed any request.

XVI. The objections of the appellant, in so far as relevant to the present decision, are summarised as follows.

Clarity:

- The subject-matter of claim 1 was unclear, since it required the same buffer to be used in steps b) and c) but at the same time required different pH values.

- It was unclear to the skilled person whether an intermediate pH adjustment step was included.

- The same objections applied to claim 7 and to the dependent claims 4, 5, 10 and 11.

Sufficiency of disclosure:

- A number of features of claim 1 did not allow the skilled person to carry out the claimed invention without undue burden.

- The same applied to claims 4 and 5.

- Also, the terms "*several*" in claim 2 and "*fermentation broth*" in claim 7 were not defined in the patent and gave rise to an insufficiency of disclosure.

Novelty:

- Example 9 of F1 disclosed a process comprising all the features of claim 1 and was thus novelty-destroying for the subject-matter of claim 1.

Inventive step:

- F1, especially its example 9, represented the closest prior art.

- The only possible feature distinguishing the claimed process from F1 was the pH of the elution buffer used in step c).

- It would have been obvious to the skilled person to acidify the buffer to be used for elution from the second reverse phase chromatography column, since an acidification step to a pH value of 3.5 was disclosed in example 9 of F1 itself. Moreover, an acidification aiming at increasing purity was also obvious in view of F2.

- It had to be concluded that the subject-matter of claim 1 lacked inventive step.

XVII. The arguments of the respondent, in so far as relevant to the present decision, can be summarised as follows.

Clarity:

- The subject-matter of the claims of the main request derived from the claims as granted. As such, the main request was not open to clarity objections, see decision G 3/14.

- Even considering the clarity objections raised, they were not founded. Claims 1 and 7 did not

require the use of an identical buffer in steps b) and c) except for it being aqueous alcohol.

Sufficiency of disclosure:

- The claimed subject-matter was defined in the patent in a manner clear and complete.

- In particular, the examples of the patent gave clear guidance to the skilled person, thus enabling the claimed process to be carried out without any difficulty.

- The burden of proof as regards sufficiency of disclosure lay with the appellant, which did not provide any evidence that the claimed process could not be carried out.

Novelty:

- Example 9 of F1 did not disclose the pH of the buffer used for elution in the second reverse phase chromatography step.

- The subject-matter of the main request was thus novel.

Inventive step:

- Example 9 of F1 represented the closest prior art.

- The subject-matter of claim 1 differed from the process of example 9 in that daptomycin was eluted at a pH of 2.5 to 3.5 in the second reverse phase chromatography step.

- The technical effect of this distinguishing feature was that it enabled the separation of daptomycin

from the impurity represented by its β-isomer. This technical effect was supported by D10 and A001.

- Therefore, the objective technical problem was the provision of an improved method for purifying daptomycin.

- Neither F2 nor any of the other documents cited by the appellant would have prompted the skilled person to use the claimed pH in the method of F1.

- Thus, the subject-matter of the main request involved an inventive step.

XVIII. During the oral proceedings, the appellant agreed with the board that its objection raised in writing to the validity of the priority was irrelevant to these appeal proceedings in view of the fact that no document published during the priority interval had been cited by the appellant against the patent.

As a consequence, a decision of the board concerning the validity of the priority is unnecessary.

Reasons for the Decision

Main request - clarity of the claims under Article 84 EPC

1. The appellant argued that claim 1 (II above) was unclear in view of the fact that it required the same buffer to be used in steps b) and c). This was in contradiction with the further requirement of claim 1 that steps b) and c) had to be carried out at different pH values. The same objection applied to claim 7 (II above) and to the dependent claims 4, 5, 10 and 11, reciting as follows:

"*4. A process according to claim 1, wherein the elution buffer in b) and c) is aqueous ethanol.*

5. A process according to claim 4, wherein the elution buffer is 5-80% ethanol.

10. A process according to claim 7, wherein the elution buffer in c) and in step d) is aqueous ethanol.

11. A process according to claim 10, wherein aqueous ethanol is 5-80% ethanol."

During the oral proceedings, the appellant further pointed to the expressions "*comprising the steps of*" and "*containing the steps of*" as mentioned in claims 1 and 7, respectively. In view of these expressions, the claimed process was not limited to the steps mentioned. Other steps could be present. Since claims 1 and 7 required the same buffer to be used in steps b) and c), but at the same time different pH values, it was unclear to the skilled person whether an additional pH adjustment step was present between steps b) and c). This generated a lack of clarity.

2. The respondent brought forward that claims 1 and 7 of the main request represented a combination of granted claims and, therefore, they were not open to clarity objections in view of decision G 3/14 (OJ EPO, 2015, 102).

3. The board takes the view that even considering the clarity objections raised by the appellant, these are not convincing for the following reasons.

3.1 Claim 1 (II above) contains the following wording:

"*the elution buffer in b) and c) is aqueous alcohol; the first reverse phase chromatography column is eluted*

at pH 6.5-8.5; and the second reverse phase chromatography column is eluted at pH 2.5-3.5".

Analogous wording is used in claim 7 (II above).

3.2 This wording does not require that the **same** elution buffer be used in steps b) and c). It merely requires that the elution buffer in b) and c) "*[be] aqueous alcohol*". The board understands this feature as meaning that the elution buffer to be used in steps b) and c) has to contain water and alcohol. However, further substances can also be present, giving rise to the required different pH values.

Claim 1 makes clear that elution buffers having different pH values are used for elution in steps b) and c) respectively. The fact that claim 1 does not specify how this is carried out, by means of an intermediate pH adjustment step or in any other way, does not give rise to any lack of clarity. On the contrary, this merely means that claim 1 covers processes with or without such a pH adjustment step.

3.3 Therefore, the board concludes that claim 1 is clear within the meaning of Article 84 EPC. The same conclusion applies *mutatis mutandis* to claim 7 and to the dependent claims 4, 5, 10 and 11.

3.4 Thus, the main request complies with Article 84 EPC.

Main request - sufficiency of disclosure under Article 83 EPC

4. According to the appellant, a number of features of the claims of the main request did not allow the skilled person to carry out the claimed invention without undue burden.

4.1 The term "*partly purified*" as mentioned in step a) of claim 1 was not defined in the patent, so the skilled person did not know which daptomycin solution had to be used in step a). Moreover, the act of "*loading*" in steps a), b) and c) did not allow daptomycin to be purified. It was further not specified how the product should be removed from the anion exchange chromatography column to be loaded in step b). Additionally, the feature "*the elution buffers*" lacked an antecedent with respect to steps a), b) and c). Finally, a same buffer might not have different pH values without an intermediate pH adjustment step, which, however, was not mentioned in claim 1.

4.2 The last objection also applied to claims 4, 5 and 7. They too required the same buffer to be used in steps b) and c) despite the additional requirement of different pH values.

4.3 Claim 2 contained the term "*several*". The patent did not contain any definition of this term, thus the starting material to be used in the claimed purification process could not be determined without ambiguity.

4.4 Additionally, the term "*fermentation broth*" mentioned in step a) of claim 7 was not defined in the patent, thus leading to a further insufficiency problem. The skilled person did not know what was meant by this term.

5. The board notes that for a claimed invention to be insufficiently disclosed within the meaning of Article 83 EPC, there must be serious doubts, substantiated by verifiable facts, that the claimed invention cannot be carried out by the skilled person without undue burden.

The board holds that the appellant has not provided any verifiable facts able to cast doubt on the sufficiency of disclosure of the claimed subject-matter, and this for the following reasons.

5.1 It is acknowledged that the feature of claim 1 "*solution comprising partly purified daptomycin*" is broad and does not define the composition of the solution loaded in step a) onto the anion exchange chromatography column, apart from the fact that it comprises daptomycin. However, the mere fact that a feature is broad is not in itself a ground for considering a claimed subject-matter insufficiently disclosed. In the case at issue, the skilled person would immediately recognise that any solution containing daptomycin in combination with other substances would have been "*partly purified*" within the meaning of claim 1.

Additionally, sufficiency of disclosure must be assessed with respect to the patent as a whole. The patent discloses, e.g. in paragraph [0021] and example 2 (paragraphs [0045] to [0050]), how to obtain a "*solution comprising partly purified daptomycin*" to be subsequently loaded onto an anion exchange chromatography column as required by step a) of claim 1 at issue.

Therefore, the term "*partly purified*" in claim 1 does not result in any insufficiency of disclosure of the claimed subject-matter.

5.2 Claim 1 (II above) defines a process in which daptomycin is purified by means of at least three chromatographic steps, specifically step a) consisting of anion exchange chromatography and steps b) and c) consisting of reverse phase chromatography.

As already mentioned under point 6.2.2 of the board's communication issued in preparation for the oral proceedings (VIII above), and not disputed by the appellant, a person skilled in the art of chromatographic purification of compounds is well aware that the compound to be purified (here daptomycin) is first *loaded* onto the chromatographic column and that this step of *loading* does not allow any purification as such. Claim 1 then requires specific *elution buffers* to be used in steps a) to c). The mention of elution buffers renders immediately clear to the skilled person that the compound to be purified has been fixed onto the chromatographic column during the previous *loading* and is then *eluted* from the column by means of the elution buffers referred to, thus allowing the compound purification. No other details than those mentioned in claim 1 are needed for carrying out the claimed process.

5.3 As mentioned under 3 above, claim 1 does not require the same buffer to be used in steps b) and c), but merely that the elution buffers used in steps b) and c) both contain water and alcohol. How the mentioned different pH values for the elution buffers to be used in steps b) and c) are obtained, by means of an intermediate pH adjustment step or in any other way, is irrelevant.

5.4 Even assuming, *arguendo*, that the skilled person would have had doubt as to how the claimed chromatographic steps should be carried out, the patent discloses in paragraphs [0023] to [0031] and in examples 1 and 2 detailed ways to perform the claimed process.

5.5 The board thus concludes that the subject-matter of claim 1 is sufficiently disclosed in the patent.

5.6 As regards the objections to claims 4, 5 and 7, the same observations mentioned under 5.3 above apply. Claims 4, 5 and 7 do not require that the same elution buffer be used in the two reverse phase chromatography steps, but merely that the elution buffers be "*aqueous alcohol*" (claim 7), "*aqueous ethanol*" (claim 4) and "*5-80% ethanol*" (claim 5). This requirement does not imply that the buffers must also have the same pH.

Even assuming that the skilled person would have had doubts as regards the buffers to be used, examples 1 and 2 clarify that the elution buffers in steps b) and c) are both based on aqueous ethanol but they have different pH values.

5.7 Claim 2 refers to the process of claim 1 "*wherein one or several clarification steps is performed prior to the anion exchange chromatography step a)*".

The patent discloses, e.g. in paragraph [0021] and example 2 (paragraphs [0045] to [0050]), the clarification step(s) that can be performed prior to the anion exchange chromatography step a) in accordance with claim 2. In view of this disclosure, the feature "*one or several clarification steps*" of claim 2 does not present any ambiguity, let alone insufficiency for the skilled person.

5.8 The term *fermentation broth* as used in step a) of claim 7 does not present any ambiguity for the skilled person either. In fact, a fermentation broth is the broth issued by a fermentation process. The patent explains in paragraphs [0002] to [0004] that daptomycin is typically produced by fermentation of *Streptomyces roseosporus.* Paragraph [0021] then discloses that a *fermentation broth* is used as the starting material of the claimed process. This broth is thus produced by

fermentation and comprises the daptomycin to be purified.

5.9 For the reasons set out above, the board concludes that the subject-matter of the main request is sufficiently disclosed in the patent, thus meeting the requirements of Article 83 EPC.

Main request - novelty under Article 54 EPC

6. The appellant argued that the subject-matter of claim 1 lacked novelty over the disclosure of document F1. It especially referred to example 9 of F1, which disclosed a process for purifying daptomycin comprising all the features of claim 1 at issue.

7. The board disagrees for the following reasons.

7.1 Example 9 of F1 (column 34) discloses a process for purifying a daptomycin preparation. According to the disclosed procedure, after

- elution from an FP-DA13 column (anion exchange chromatography column, F1, column 31, lines 1 to 2) at pH 6.5-7.0 (corresponding to step a) of claim 1),

- the daptomycin is loaded onto an equilibrated HP-20ss column (reverse phase chromatography column, F1, column 31, line 6). After a washing step, daptomycin is eluted from the column with an elution buffer consisting of 25% isopropyl alcohol/ 60 mM acetate at pH 6.6 (corresponding to step b) of claim 1).

- Eluted daptomycin is adjusted to pH 3.5 with 0.25 M phosphoric acid and reloaded onto the HP-20ss column to enhance purity. According to example 9 of F1, the column is then "*washed with a pH adjusting*

buffer ***such that the pH is 6.5***" (emphasis added by the board). The daptomycin is then "*eluted with* ***elution buffer***" (corresponding to step c) of claim 1, emphasis added by the board) and may be further purified if desired.

Contrary to the appellant's view, the elution buffer used to elute daptomycin in the second reverse phase chromatography step (last step above) is not disclosed in example 9 of F1, let alone its pH.

7.2 Solely for this reason, the subject-matter of claim 1 is novel over the disclosure of F1 invoked by the appellant.

7.3 The same reasoning applies *mutatis mutandis* to the subject-matter of independent claim 7, which is also novel over the mentioned disclosure of F1.

7.4 The board concludes that the subject-matter of claims 1 and 7, and of the dependent claims 2 to 6 and 8 to 11, is novel within the meaning of Article 54 EPC.

Main request - inventive step under Article 56 EPC

8. The closest prior art

8.1 Both parties indicated F1 as the closest prior art for the claimed subject-matter.

8.2 In view of the issues addressed and the purification process disclosed, the board agrees that F1 represents a suitable starting point for the assessment of inventive step. In fact, F1 (column 3, line 47 to column 4, line 1 and claim 1) concerns a process for the chromatographic purification of daptomycin, whereby the major impurities, anhydro-daptomycin and β-isomer, are removed and a daptomycin purity of at least 98% is

achieved. These are the same aims as stated in the patent (paragraphs [0017] and [0018]).

8.3 Especially in its example 9 (7.1 above), F1 discloses a process for the purification of daptomycin comprising three steps which correspond to steps a) to c) as mentioned in claim 1 at issue.

8.4 As set out above in the discussion on novelty, the subject-matter of claim 1 differs from example 9 of F1 at least in that:

- the reverse phase chromatography column in step c) is eluted with an aqueous alcohol elution buffer at pH 2.5 to 3.5.

In fact, the elution buffer used to elute daptomycin in the second reverse phase chromatography step is not reported in example 9 of F1, let alone its pH.

9. The technical problem

9.1 The appellant did not identify the above-mentioned distinguishing feature to be present (see novelty objection mentioned above) and argued that the only possible technical problem to be solved over F1 was the provision of an alternative elution buffer.

9.2 However, in view of the board's novelty assessment above, the technical problem has to be formulated by taking into account the technical effect of the above-mentioned distinguishing feature.

9.2.1 In this respect, the respondent referred to D10 (experiments 1 and 2 refiled with its reply to the statement of grounds of appeal; page 10, tables 1 and 2) and to experimental report A001.

9.2.2 The board notes that in experiments 1 and 2, a substantially identical daptomycin solution containing about 94% daptomycin and 2.5% β-isomer impurity was loaded onto the same reverse chromatography column. In experiment 1 the elution from this column in the second reverse phase chromatography step (corresponding to step c) of claim 1) was performed with an aqueous ethanol buffer at pH 6.4 (i.e. above the upper limit of the range defined in claim 1). In experiment 2 the same elution buffer, but acidified at pH 3, was used, in accordance with the pH range as required by claim 1 at issue (2.5 to 3.5).

The results show that by using the elution buffer at pH 3, the β-isomer impurity could be removed, whereas it was still present when the elution was carried out at pH 6.4. Moreover, daptomycin purity was increased (97% vs 94.7%, tables 1 and 2).

The respondent (pages 9 and 10 of the reply to the statement of grounds of appeal) explained this result by referring to the different pKa values of the β-aspartyl group of the β-isomer and the aspartyl group of daptomycin.

9.2.3 In A001 the respondent reworked example 9 of F1. As starting material for the first reverse phase chromatography step, the respondent (reply to the statement of grounds of appeal, page 11, point 6.3) used a daptomycin solution prepared according to example 2 of the patent (paragraphs [0045] to [0047]), i.e. as obtained after the same pre-clarification steps and anion exchange chromatography.

In view of the lack of information concerning the elution buffer used in the second reverse phase chromatography step (7.1 and 8.4 above) of example 9 of

F1, the respondent used the same buffer as for the elution in the first reverse phase chromatography step, i.e. 25% isopropyl alcohol/60 mM acetate at pH 6.6 (7.1 above). The board concurs that this is the most probable interpretation of the disclosure of example 9 and the best way to rework it.

The results show that neither reduction in the content of β-isomer nor improvement in the daptomycin purity was obtained.

9.2.4 On the basis of these experimental results, the board is convinced that the above-identified distinguishing feature, i.e. a pH value of 2.5 to 3.5 of the elution buffer used in the second reverse phase chromatography step, results in a reduction of the β-isomer impurity.

9.3 Thus, the objective technical problem lies in the provision of a process as disclosed in F1, whereby the content of the β-isomer impurity is reduced.

10. Obviousness of the claimed solution

10.1 It remains to be assessed whether the claimed solution would have been obvious to the skilled person with regard to F1, possibly in combination with other documents on file. In this respect, the appellant referred in writing to documents F2 to F4 and F6 to F11. However, during the oral proceedings, the appellant only relied on document F2 for the question of obviousness.

10.2 In fact, the board notes that among the documents cited by the appellant, only F2 relates to the purification of daptomycin. The other documents are either very general disclosures about reverse phase chromatography (F9 to F11) or they concern the chromatographic purification of specific compounds different from

daptomycin (F3, F4 and F6 to F8). Therefore, documents F3, F4 and F6 to F11 are not relevant for the question of obviousness of the claimed subject-matter in view of F1. This view, already expressed by the board under point 8.3.2 of its communication (VIII above), was not contested by the appellant during the oral proceedings.

10.3 The appellant put forward that the claimed solution to the posed technical problem was obvious in view of the document F2. In fact, F2 disclosed the use of an acidified ethanol buffer for the elution of daptomycin.

10.4 The board disagrees for the following reasons.

10.4.1 Document F2 discloses (column 1, lines 47 to 55; column 2, line 61 to column 3, line 32) a process for the purification of daptomycin (referred to in F2 as antibiotic LY146032) comprising adsorbing daptomycin onto a non-functional resin, followed by physically removing the water from the resin, re-wetting the resin with a polar organic solvent and eluting the product by increasing the polarity of the solvent. F2 (column 3, lines 48 to 61) discloses that, *inter alia*, ethanol can be used as the solvent and that acidification to a pH of 4 to 5 increases the resolution of the process and reduces the formation of transpeptidation by-products. Though referring to the removal of impurities in general (column 2, lines 40 to 45), F2 does not mention the β-isomer of daptomycin. A final purity of 80% to 93% is reported (column 2, lines 40 to 45 and example 1).

10.4.2 As mentioned under 8.2 above, F1 is concerned instead with the removal of the β-isomer impurity and the achievement of a daptomycin purity of at least 98%. In referring to F2, F1 (column 2, lines 30 to 56) states that the method described in F2 only allowed a

daptomycin purity of 80% to 93%, while the impurities present in the daptomycin preparation, i.e. anhydro-daptomycin and β-isomer, were not disclosed in F2.

10.4.3 Therefore, the skilled person seeking a solution to the posed technical problem would not have had any incentive to modify the process of F1, especially its example 9, by combining it with the method taught in F2. Moreover, the acidification taught in F2 is to a pH value of 4 to 5 (10.4.1 above), i.e. outside the range of 2.5 to 3.5 as required by claim 1 at issue.

10.5 The appellant also argued that the use of an acidic pH was obvious in view of example 9 of F1 itself. Here F1 taught acidifying the daptomycin solution to pH 3.5 after the first reverse phase chromatography step and before the second reverse phase chromatography step, thus suggesting the claimed solution.

10.6 However, as already stated under 7.1 above, example 9 of F1 (column 34, lines 21 to 24) discloses adjusting the pH of the daptomycin solution eluted from the first reverse phase chromatography column to pH 3.5 before reloading the solution onto the reverse phase chromatography column. However, the column is then "*washed with a pH adjusting buffer* ***such that the pH is 6.5***" (emphasis added by the board). Only after that does daptomycin elution take place. Therefore, the acidification to a pH value of 3.5 is carried out in example 9 of F1 for *loading* and not for *eluting* daptomycin. As set out above, no indication is given in example 9 of F1 as regards the pH used for elution in the second reverse phase chromatography step.

10.7 When aiming at solving the posed technical problem, the skilled person would have rather considered the teaching of e.g. example 2 of F1. Here a 99% pure

daptomycin was obtained while β-isomer was undetectable (column 31, lines 20 to 44).

However, by following the process of example 2, the skilled person would not have arrived at the subject-matter of claim 1. In fact, example 2 of F1 (*loc. cit.*) teaches first purifying a daptomycin preparation as disclosed in F2, whereby at least 1% β-isomer still remains (impurity 8 as identified in example 10 of F1, column 35, lines 30 to 33), and then loading the resulting solution onto an anion exchange resin, eluted with a NaCl buffer at pH 7.0. Therefore, the process of example 2 of F1 is completely different from the process of claim 1 at issue.

10.8 Consequently, the skilled person would not have been prompted by F1 or the other documents invoked by the appellant to modify the process disclosed in example 9 of F1 so as to arrive at the subject-matter of claim 1. The same reasoning applies *mutatis mutandis* to the subject-matter of claim 7.

10.9 Thus, the board concludes that the subject-matter of claims 1 and 7, and of the dependent claims 2 to 6 and 8 to 11, involves an inventive step within the meaning of Article 56 EPC.

Conclusion

11. The main request of the respondent is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated