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Datasheet for the decision of 2 February 2023

Case Number: T 0045/21 - 3.3.07

Application Number: 10832379.1

Publication Number: 2504353

IPC: A61K9/19, A61K38/12, A61P31/04, A61K9/08, A61K38/00, A61K47/18, A61K47/26, C07K11/02, A61P17/00, A61P31/00

Language of the proceedings: EN

Title of invention:
LIPOPEPTIDE COMPOSITIONS AND RELATED METHODS

Patent Proprietor:
Cubist Pharmaceuticals LLC

Opponents:
HGF Limited
Pajaro Limited

Headword:
Lipopeptide compositions / CUBIST

Relevant legal provisions:
EPC Art. 123(2), 83, 54, 56

Keyword:

Amendments - added subject-matter (no)
Sufficiency of disclosure - relationship between Article 83 and Article 84
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

T 0415/11, T 0815/07, T 2096/12, T 1845/14, G 0003/14

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Case Number: T 0045/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 2 February 2023

Appellant: (Opponent 2)	Pajaro Limited 12 New Fetter Lane London EC4A 1JP (GB)
Representative:	Bird & Bird LLP Maximiliansplatz 22 80333 München (DE)
Respondent: (Patent Proprietor)	Cubist Pharmaceuticals LLC Weystrasse 20 6000 Lucerne 6 (CH)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Party as of right: (Opponent 1)	HGF Limited Saviour House 9 St Saviour Gate York YO1 8NQ (GB)
Representative:	Dentons UK and Middle East LLP One Fleet Place London EC4M 7WS (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 November 2020 concerning maintenance of the European Patent No. 2504353 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	L. Basterreix

Summary of Facts and Submissions

I. Two oppositions were filed against the patent in suit. The appeal was filed by opponent 2 (the appellant) against the interlocutory decision of the opposition division finding that, on the basis of the main request filed on 9 October 2019, the patent met the requirements of the EPC.

II. Claim 1 of this main request read as follows:

"A solid daptomycin composition, wherein said composition is prepared by lyophilizing an aqueous liquid daptomycin solution comprising at least one excipient which is a non-reducing sugar, wherein the aqueous liquid daptomycin solution has a pH of 6.5 to 7.5."

III. The following documents, among others, were cited in the appealed decision:

P1: US 61/263,784 (priority application)
D1: WO 2011/062676 A1
D2: Franks, European Journal of Pharmaceutics and Biopharmaceutics 1998, 45(3):221-229
D4: Wang, International Journal of Pharmaceutics 2000, 203(1-2):1-60
D7: EP 0 386 951 A2
D8: WO 2007/061529 Al
D9: Carpenter et al., Pharmaceutical Research 1997, 14(8): 969-975
D10: WO 2008/012310 A1
D11: WO 2009/002481 A1
D12: US 5,952,300

D16: Carpenter J.F. et al., "Rational design of stable lyophilized protein formulations: theory and practice" Kluwer Academic, 2002, 109-133
D20: Cubicin® EPAR, Scientific Discussion, 2006
D29: Declaration of Prof. Geoffrey Lee

IV. The opposition division decided that the main request did not contain added subject-matter, and that any ambiguity as to the pH measurement was not enough in itself to deny sufficiency of disclosure. The subject-matter of the main request was novel over both D1 and D7, and involved an inventive step starting from the Cubicin® formulation as closest prior art.

V. With the statement setting out the grounds of appeal, the appellant filed documents A049-A051:

A049: Seven2Go pH Meter operating instructions by Mettler Toledo
A050: InLab Micro Pro-ISM specifications by Mettler Toledo
A051: T 0415/11

VI. In reply to the appeal, the patent proprietor (respondent) defended their case on the basis of the main request upheld by the opposition division (see II. above), and on the basis of auxiliary requests 1-51.

The respondent further filed documents A052 and A053:

A052: Second declaration by E. Topp (including Appendix A-C)
A053: Final Report - pH Measurement of Daptomycin Solutions

VII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VIII. Oral proceedings took place before the Board.

IX. The appellant requests that the decision under appeal be set aside and that the patent be revoked in its entirety. The appellant also requests that claim requests that are non-converging, and auxiliary requests 7-45, be not admitted. The appellant further requests that auxiliary requests 46-51 be rejected for being unsubstantiated.

X. The respondent requests that the appeal be dismissed and that the patent be maintained on the basis of the main request, or, alternatively, on the basis of one of the following auxiliary requests:
- auxiliary requests 1-6 filed on 9 October 2019,
- auxiliary requests 7-45 filed on 21 July 2020, or
- auxiliary requests 46-51 filed with the reply to the appeal.

The respondent also requests that A049 and A050 be not admitted into the proceedings. In the event that A049 and A050 are admitted into the proceedings, the respondent requests that A052 and A053 be admitted into the proceedings.

XI. Opponent 1 is party as of right and did not make any submission in the appeal proceedings.

XII. The appellant's arguments regarding the main request were essentially the following:

(a) Claim 1 of the main request resulted from several selections and undisclosed combinations of features

in the application as filed. Claim 1, as well as claims 3, 4, 6, 8, 11, and 12, contravened Article 123(2) EPC.

(b) Regarding the feature of claim 1 relating to the pH of 6.5 to 7.5, the patent did not disclose the temperature for the measurement of the pH. As a result, the criteria of sufficiency of disclosure were not met.

(c) The subject-matter of claim 1 of the main request lacked novelty over D1 and D7.

(d) Starting from the Cubicin® formulation as closest prior art, the distinguishing features were the non-reducing sugar and the pH of 6.5 to 7.5. These differentiating features neither led to improved reconstitution times, nor to improved stability. But even if the problem was seen in the provision of an improved formulation, the claimed formulation was rendered obvious by the common general knowledge, by D7, or by the prior art related to caspofungin. Alternatively, the subject-matter of claim 1 lacked an inventive step starting from D7 or from D8

XIII. The respondent's arguments regarding the main request were essentially the following:

(a) The documents A049 and A050 were not to be admitted, because they were late filed and not *prima facie* relevant.

(b) The combination of features of claim 1 of the main request, as well as the dependent claims, found basis in the application as filed.

(c) The patent enabled the skilled person to provide a pharmaceutical composition according to claim 1 regardless of the ambiguity on the pH range of 6.5-7.5 alleged by the appellant. The criteria of sufficiency of disclosure were met.

(d) Neither D1 nor D7 disclosed solid compositions obtained by lyophilising an aqueous composition comprising daptomycin and a non-reducing sugar at a pH of 6.5-7.5. The criteria of novelty were met.

(e) Cubicin® was the most promising starting point. The differentiating features were the non-reducing sugar and the higher pH of 6.5-7.5. The objective technical problem was the provision of an improved solid daptomycin composition, i.e. having improved chemical stability and reconstitution time. The claimed solution involved an inventive step. This conclusion was not changed when starting alternatively from D7 or D8.

Reasons for the Decision

The present decision is based on the respondent's main request (see II. above), which is the request allowed by the opposition division.

1. Article 123(2) EPC

1.1 Claim 1 of the main request pertains to a solid daptomycin composition prepared by lyophilizing an aqueous liquid daptomycin solution comprising at least one excipient which is a non-reducing sugar, wherein

the aqueous liquid daptomycin solution has a pH of 6.5 to 7.5.

1.2 The use of a pH of 6.5-7.5 is disclosed on page 3, lines 23-26, of the application as filed. This pH range is disclosed in the context of lipopeptides in general. However, the application as filed as a whole discloses that daptomycin is the preferred lipopeptide (see in particular page 1, lines 8-12; page 3, lines 9-14; and the examples, which are all directed to daptomycin compositions). Contrary to the appellant's view, the disclosure of the pH range on page 3 is neither limited to sugar-free compositions (which are just mentioned by way of example in lines 26-30) nor is it inextricably linked to a step of "increasing the pH", since the skilled person would appreciate that the desired accelerated reconstitution is obtained by adjusting the pH to the stated preferred range, the "increasing" step merely referring to the fact that daptomycin would otherwise lead to a lower pH (see page 3, lines 26-30 and page 8, line 29).

The presence of a non-reducing sugar is disclosed e.g. on page 3, lines 31-33. This disclosure is not to be seen as an embodiment which is separate from the above mention of the pH range of 6.5-7.5, but as a further measure which also contributes to accelerated reconstitution. The fact that the disclosure on page 3, lines 31-33, is made in the context of the first embodiment mentioned on page 3 (lines 23-26) is confirmed by the fact that a second embodiment is only mentioned later, at the bottom of page 4. The combination of claim 1, namely lyophilisation of a daptomycin solution comprising a non-reducing sugar and a pH of 6.5-7.5, is further supported by page 8, lines 25-32. In this respect, the Board concurs with the

appealed decision (see paragraph 2.1.3) that lyophilization is the preferred drying method. The preference for a non-reducing sugar as excipient is explicit on page 8, line 32, and is consistent with the examples.

1.3 Dependent claims 3, 4, 6 and 8 further specify the non-reducing sugar to be trehalose, sucrose and mannitol. These sugars are recited in the application as filed, e.g in the paragraph bridging pages 8-9, and neither the limitation to a shorter list in claim 3, nor the single selection of one of the sugars in each of claims 4, 6 and 8, lead to the singling out of any undisclosed combination.

Claim 11 and 12 specify the presence of a sodium phosphate buffering agent or sodium phosphate dibasic. The Board agrees with the opposition division (see the appealed decision, page 19) that these buffering agents result from single selections from the list on page 8 of the application as filed, which does not contravene Article 123(2) EPC.

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

2. Sufficiency of disclosure

2.1 According to the appellant, the invention is insufficiently disclosed because the patent does not teach the temperature at which the pH is to be determined. The appellant relies on several documents, including A049 and A050 filed with the grounds of appeal, to show that, depending on the temperature at which it is measured, i.e. from 2°C to 10°C or 25°C, the pH could vary by up to 0.2 pH units. The appellant,

citing T 815/07 and T 2096/12, reasons that the pH is essential to obtain the sought improvements in reconstitution time and stability, and that, as a result of the lack of indication of the temperature for its measurement, the skilled person does not know whether he is working within the claimed scope or not.

2.2 For the purposes of the present decision, it is not necessary to establish whether the measured pH indeed varies to such an extent depending on the temperature for the measurement. It is also not necessary to detail the reasons why the Board admitted the evidence A049 and A050. This is because, in any case, the appellant did not demonstrate that this variation would prevent the skilled person from reproducing the invention without undue burden.

2.3 Firstly, the appellant's arguments regarding the possibility (for the person skilled in that art) to know at which temperature the pH is to be determined, or how to carry out the invention as meant by patentee (as argued by the appellant, see the grounds of appeal, §54 and §60) do not go beyond questioning the boundaries of the claim and emphasizing the error margin in the pH range defining the claimed daptomycin composition.

However, the assertion that the skilled person is unable to determine whether he is working within the claimed scope as such is not a valid basis for denying sufficiency of disclosure. It is for that matter not relevant that, as a result of the lack of indication of the measurement temperature, the pH variation (up to 0.2°C) may amount to 20% of the claimed range (6.5-7.5). The mere fact that a degree of variability exists in a claimed parameter cannot as such lead to a

finding of insufficiency of disclosure, if the influence of this variability on the possibility for the skilled person to carry out the claimed invention has not been established, namely in the present case to prepare a daptomycin composition as claimed.

The Board agrees with the appellant that the patent proprietor must not benefit from any lack of clarity in the patent. This is however not to say that such a lack of clarity must, on its own, necessarily lead to the rejection of the claim request or revocation of the patent for lack of sufficient disclosure. As explained in G 3/14 (see point 55 of the reasons), a granted claim may turn out not to comply with Article 84 EPC but such non-compliance must be lived with. To the extent that the alleged pH variation by up to 0.2 units leads to a lack of clarity, the appellant has not shown the effect of this lack of clarity on the assessment of sufficiency of disclosure.

2.4 Secondly, the appellant argues that the pH is essential to obtain the sought improvements in reconstitution time and stability.

However, the requirement of sufficiency of disclosure relates to the invention defined in the claims. An objection of insufficient disclosure under Article 83 EPC cannot legitimately be based on an argument that the application would not enable a skilled person to achieve a non-claimed technical effect (Case Law of the Boards of Appeal, 10th edition, 2022, II.C.3.2). The Board shares the view, expressed in T 1845/14, that in case of an unclear parameter defined in a claim whose values required in the claim are indicated in the specification to be essential to solving the problem underlying the patent at issue, the ability of the

skilled person to solve that problem by reproducing what is claimed is not a suitable criterion for assessing sufficiency of disclosure when the problem or an effect derivable from it are not explicitly or implicitly part of the definition of the claimed subject-matter (see point 9.8 of the reasons). This view has been endorsed by subsequent case law (see the Case Law of the Boards of Appeal, 10th edition, 2022, II.C.5.5.1).

2.5 In the present case, claim 1 does not explicitly require that the solid daptomycin composition exhibit any properties with respect to reconstitution time and stability. Claim 1 mandates that the composition be prepared by lyophilizing an aqueous liquid daptomycin solution having a pH of 6.5 to 7.5. The appellant does not contest that the pH is a usual parameter. To the extent that the pH may vary by up to 0.20 units depending on the measurement temperature, this possible issue must be resolved by interpreting the claim. The alleged pH variation does not call for a narrow interpretation whereby some defined reconstitution time and stability properties would be read into the claim. On the contrary, the Board considers that, since claim 1 sets no limitation as to the temperature for the pH measurement, then the claim must be given its broadest technically meaningful interpretation: claim 1 covers compositions prepared by lyophilizing a solution having a pH of 6.5-7.5 under any of the temperatures considered (here, from 2°C to 25°C).

Accordingly, the question of sufficiency of disclosure is whether the skilled person, on the basis of the information provided in the patent specification and, if necessary, using common general knowledge, would be able to carry out the invention as claimed, without

undue burden, over this broadly interpreted claimed range. In the present case, the appellant presented no evidence or argument that, as a result of the alleged pH variation of 0.2 units, claim 1 would cover compositions which the skilled person would be unable to prepare without undue burden.

2.6 Accordingly, the claimed invention is sufficiently disclosed.

3. Novelty

3.1 Novelty over D1

The respondent does not contest the opposition division's finding that the main request is not entitled to the priority right from P1 (see paragraph 4.3 of the appealed decision). The relevant date is therefore the filing date, namely 23 November 2010, and D1, published on 26 May 2011 and filed on 17 September 2010, belongs to the prior art under Article 54(3) EPC.

D1 (see page 12 lines 8-12) discloses kits including a "lyophilizate of daptomycin and about 5% trehalose and a pharmacologically suitable fluid with calcium hydroxide in an amount sufficient to maintain the composition at a pH of about 6.75 and arginine in an amount sufficient to maintain the composition at a pH of about 6.75".

The appellant argues that the claimed subject-matter lacks novelty over D1 because:
- the expression "the lyophilizate of daptomycin and about 5% trehalose" refers to a solid composition

prepared by lyophilizing a solution comprising both daptomycin and trehalose, and
- in the expression "fluid [...] to maintain the composition at a pH of about 6.75", the term "maintain" is used in the sense of "to cause to continue a condition". Since the lyophilizate upon reconstitution with the fluid has a pH of 6.75, this would mean that it was created from a solution at a pH of 6.75.

The Board does not agree with the appellant that the term "maintain" in D1 unambiguously indicates that the pH before lyophilisation was already at 6.75. The term is instead understood such that the pH of the composition is maintained going forward, i.e. it is maintained to 6.75 for a certain time *after* reconstitution. This is consistent with the general disclosure of D1, which relates to storage-stable liquid daptomycin compositions with said pH (see claim 1 and page 2, first paragraph under "Summary of the invention"). The kit is used to prepare this storage-stable liquid composition by reconstituting the lyophilisate and trehalose with the fluid so as to maintain the pH in the resulting liquid composition.

Hence, D1 does not disclose that the composition was prepared by lyophilizing an aqueous liquid daptomycin solution having a pH of 6.5 to 7.5. At least for this reason, D1 does not anticipate the subject-matter of claim 1 of the main request.

3.2 Novelty over D7

D7 discloses on page 4 (lines 11-14) the reconstitution of "freeze-dried daptomycin (150 mg) and 50 mg mannitol (50 mg)" in 10 ml of each buffer shown in table 1. According to the appellant, the skilled person would

understand from this expression that the freeze-dried lyophilizate comprises both daptomycin and mannitol together.

In the Board's opinion, it can be understood from this passage of D7 that mannitol and the freeze-dried daptomycin are separately present upon reconstitution with the buffer. This passage does not clearly and unambiguously indicate that the mannitol is present in the freeze-dried daptomycin.

As to the passage on page 8, line 56, to page 9, line 3, the sentence "daptomycin may be packaged with a suitable amount of buffer so that upon reconstitution with a (non-buffered) diluent, the resulting reconstituted formulation will also have a pH in the range of about 6 to about 8" does not necessarily mean that daptomycin is lyophilized with the buffer, but merely refers to their packaging together, for instance in two separate containers as foreseen in claim 7 of D7.

Hence D7 does not disclose a solid daptomycin composition prepared by lyophilizing an aqueous liquid daptomycin solution comprising a non-reducing sugar and having a pH of 6.5 to 7.5.

3.3 Accordingly, the main request meets the requirements of novelty.

4. Inventive step

4.1 Starting from Cubicin®

4.1.1 Closest prior art and differences

The commercially available product Cubicin® is a solid daptomycin composition prepared by lyophilization of an aqueous liquid daptomycin solution having a pH of 4.7 (see D20, page 3/40).

The features distinguishing the subject-matter of claim 1 from Cubicin® are
- the presence of a non-reducing sugar and
- the pH of 6.5 to 7.5
in the aqueous daptomycin solution before lyophilization.

4.1.2 Technical effects

According to the respondent, the claimed invention achieves both an improved chemical stability rate in the solid form (see paragraphs [0001] and [0021] of the patent), and an improved reconstitution time (see paragraphs [0013] and [0018]).

(a) Regarding the effect on reconstitution time, tables 6 and 7 of the patent (see figures 5 and 6 on pages 24-30) show reconstitution times of:
- 5 min for Cubicin®, i.e. daptomycin at pH 4.7 without sugar or glycine (Table 7, formulation "00"),
- 1.4 min for daptomycin at pH 7.0 without sugar or glycine (Table 6, formulation "0"), and
- below 1 min for all compositions prepared with both a non-reducing sugar and a pH of 7.0.

The Board thus accepts that the pH of 7.0 and the non-reducing sugar are each associated with an improvement in reconstitution time. In this respect, a comparison with compositions comprising reducing sugars is not relevant here, because it is

not a comparison with the closest prior art, which is a daptomycin composition prepared at pH 4.7 with no excipient.

(b) Regarding stability in solid form, table 4 on page 14 of the patent compares the chemical stability rates of compositions incorporating sugars or glycine, at a pH of 4.7 (left column) or 7.0 (right column), to a reference "Daptomycin (No Sugar or Glycine)" normalized to 1.00 in both columns. The respondent clarified that this reference composition is the same in both columns, namely daptomycin for injection corresponding to Cubicin® and prepared with a pH of 4.7.

Table 4 shows that solid compositions prepared using non-reducing sugars (trehalose, sucrose and mannitol) exhibit an improved chemical stability rate at pH 4.7 (from 1.00 to 0.16-0.95). This improvement is even larger when a pH of 7.0 is used in addition to the non-reducing sugar (i.e. from 1.00 to 0.04-0.42). Table 4 thus demonstrates that the incorporation of a non-reducing sugar in the lyophilised composition, alone or in combination with a pH of 7.0, leads to an improvement in the chemical stability in solid form.

It can be left undecided whether the pH of 7.0 alone also has a consistent effect on stability, in view of table 9 on page 39 (Figure 8) of the patent. In any case, the Board concludes that the patent credibly demonstrate that the differentiating features lead to both an improved chemical stability rate in the solid form and an improved reconstitution time.

4.1.3 Technical problem

The objective technical problem is therefore the provision of an improved solid daptomycin composition having improved chemical stability in solid form and reconstitution time.

This technical problem is credibly solved by the claimed compositions. The appellant did not provide convincing arguments or evidence calling into question the achievement of the above improvement over the pH range of 6.5-7.5, which the Board regards in these conditions as a reasonable generalisation of the tested value 7.0. This remains true even when taking into account the error margin of 0.2 pH units alleged by the appellant (see 2. above).

4.1.4 Obviousness

The relevant question is thus whether, in light of the prior art, the skilled person would have considered modifying Cubicin® by incorporating a non-reducing sugar and adjusting the pH to 6.5-7.5 prior to lyophilisation in the expectation of solving the problem, i.e. in the expectation of achieving improvements with respect to solid form stability and reconstitution time.

The document D20 describing Cubicin® already indicates that the "target in-process pH range (4.5-5.0) was selected based on the sensitivity of the active to extreme pHs" and that given "the high solubility of the active, the only excipients considered necessary were the vehicle, sodium hydroxide to achieve the target pH and nitrogen as process aid during lyophilisation. Sodium citrate and mannitol used as bulking agents for the formulation of early batches became unnecessary as

the dose for clinical use increased" (see page 3/40). In view of these statements regarding prior pharmaceutical development of Cubicin®, the skilled person has no reason to expect any of the demonstrated improvements from the use of a pre-lyophilisation pH of 6.5-7.5 or a non-reducing sugar such as mannitol.

4.1.5 The further prior art cited by the appellant does not lead to such an expectation either.

(a) D4, D9 and D16 are concerned with protein formulations. Due to their structural complexity (in particular secondary and tertiary structures), proteins present particular issues such as aggregation, denaturation or unfolding, which issues are not expected to arise in the case of the cyclic lipopeptide antibiotic daptomycin. Thus, the skilled person would not extrapolate the teaching of these documents pertaining to proteins to daptomycin, even if daptomicin is (partially) made of amino acids.

In particular, D9, a review article pertaining to stable lyophilized protein formulations, mentions e.g. sucrose or trehalose as stabilizers during the lyophilization process or to inhibit protein unfolding or denaturation during dehydration (see page 972, right column; page 973, 3rd paragraph on the left). While D9 may be relevant to proteins or polysaccharide conjugates thereof (as concluded in T 0415/11, see e.g. point 14 of the reasons), D9 provides no indication to the skilled person that the stability issues addressed in proteins by the use of such non-reducing sugars would be applicable to a cyclic lipopeptide such as daptomycin. In addition, D9 does not mention reconstitution time,

and does not disclose a pH of 6.5-7.5, but only "avoiding extremes in pH". The pH in the closest prior art (4.5-5.0) was already explicitly selected with a view to avoiding extreme pHs (see D20, page 3/40).

Likewise, the review article D4 pertains to the lyophilisation of proteins, the influence of the freezing rate on reconstitution time when using mannitol as excipient (see page 22, left), the use of sucrose and trehalose as lyoprotectants (see page 8) and the influence of the solution pH on the long-term stability of solid, lyophilized proteins (paragraph 5.4.1 on pages 44-45). D16 discloses the use of sucrose or trehalose to stabilise proteins against unfolding (see page 4, lines 1-4). For the reasons given above, the skilled person would not extrapolate these teachings to the cyclic peptide daptomycin.

Thus none of D4, D9 or D16 provide any hint as to the improvements observed in the patent when using non-reducing sugars or a pH of 6.5-7.5 in the context of lyophilized daptomycin.

(b) The review article D2 pertains more generally to "peptides, proteins, and complex synthetic organic molecules" (see §10 and the paragraph bridging pages 221 and 222) and describes the use of mannitol and sucrose as excipients or bulking agents, and of pH buffers. However, D2 does not teach any possible effect of non-reducing sugars or a pH of 6.5-7.5 on reconstitution time or solid form chemical stability.

(c) D10-D12 are limited to caspofungin, which is a different lipopeptide. As argued by the respondent (see paragraphs 7.153-7.182 of the reply dated 11 October 2021), daptomycin and caspofungin present significant differences in structure and properties, in particular regarding the main degradation pathways. Accordingly, the skilled person would not consider applying the teaching of D10-D12 to the present solid daptomycin compositions.

(d) Considering the known high solubility of daptomycin (see D20, page 3/40), there was also no reason for the skilled person to expect that the addition of hydrophilic excipients such as mannitol would have any further effect on dissolution reconstitution behaviour of lyophilized daptomycin (see the declaration D29, §31; D16, page 6, first paragraph; D2, page 223).

(e) Finally, D7 addresses the specific stability issue of daptomycin in liquid dextrose solutions. The skilled person, starting from the dextrose-free Cubicin® solid daptomycin composition would not turn to D7 and consider the use of a pH of 7.0 and mannitol in expectation of improving solid-form stability and reconstitution properties.

In conclusion, none of D2, D4, D7, D9, D10-D12 and D16 contain any suggestion that the use of the claimed non-reducing sugars and pH of 6.5-7.5 could be associated, in the case of daptomycin, with improvements in chemical stability in the solid form or reconstitution time. The question whether the skilled person had a reasonable expectation that such modifications of Cubicin® would indeed be successful is not relevant,

because the prior art does not suggest that these modifications would solve the technical problem in the first place.

4.2 Starting from D7

According to the appellant, D7 represents an alternative starting point for the assessment of inventive step.

D7 states that daptomycin, when dissolved in a 5% dextrose solution, undergoes extensive degradation. The problem underlying D7 is to provide stabilized formulations of daptomycin allowing for storage of daptomycin solutions in 5% dextrose without significant degradation. The solution proposed in D7 is to provide formulations with sufficient buffer capacity in the pH range 6-8 (see page 1, lines 37-43). In some examples of D7, the liquid composition comprises mannitol.

According to the appellant, starting from D7, the distinguishing feature is that the claimed composition is a solid composition prepared by lyophilising a daptomycin liquid composition. The objective technical problem would be the provision of an alternative stable daptomycin composition. The appellant takes the position that a skilled person would have lyophilized the solutions of D7.

However, the skilled person would not realistically follow such an approach starting from D7: in D7, lyophilized daptomycin is reconstituted with normal saline and 5% dextrose and converted into liquid daptomycin compositions, with the purpose that these liquid compositions remain stable upon storage in liquid form, i.e. until final use. The appellant's

approach, whereby the skilled person would lyophilise again these final liquid compositions and turn them into solid compositions, is thus based on hindsight. The appellant's further argument that the skilled person could also start from an intermediate product in D7 before addition of dextrose is even less realistic. Such approaches run counter to the framework defined by the choice of D7 as starting point.

Furthermore, the skilled person could not expect that the use of mannitol and a neutral pH, used in D7 to stabilise the composition in liquid form, would result in stable solutions of daptomycin once lyophilised. Such an effect of non-reducing sugars and neutral pH on solid daptomycin is not hinted at in the prior art (see 4.1.4 and 4.1.5 above).

4.3 Starting from D8

The appellant also relies on D8 as alternative starting point. D8 relates to a general lyophilisation process, and mentions daptomycin in a laundry list of several thousands active ingredients (see paragraph [0031]). Among many alternative embodiments and further measures, D8 mentions an optional adjustment of the pH to an undisclosed value (see page 9). Finally, D8 separately indicates that trehalose is a particularly suitable bulking agent, but at the same time expresses a preference for the absence of auxiliary components (see paragraph [0053]).

The Board agrees with the respondent that D8 is of a speculative nature, at least as far as daptomycin is concerned, and does not disclose the combination of daptomycin with a non-reducing sugar, let alone with a

pH of 6.5-7.5. Accordingly, D8 cannot lead to the claimed invention in an obvious manner.

4.4 In conclusion, the main request meets the requirements of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sanchez Chiquero A. Usuelli

Decision electronically authenticated