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**Datasheet for the decision  
of 29 March 2017**

**Case Number:** T 2154/14 - 3.3.04

**Application Number:** 99949913.0

**Publication Number:** 1115417

**IPC:** A61K38/12

**Language of the proceedings:** EN

**Title of invention:**

Use of daptomycin

**Patent Proprietor:**

Cubist Pharmaceuticals, Inc.

**Opponents:**

Plate Schweitzer Zounek  
Sölch, Günter

**Headword:**

Daptomycin II/CUBIST PHARMACEUTICALS

**Relevant legal provisions:**

EPC 1973 Art. 56, 87(1)  
RPBA Art. 13(1), 13(3)

**Keyword:**

Main request - inventive step (no)

Late-filed auxiliary request - admitted (no)

**Decisions cited:**

G 0002/98, G 0001/15, T 0201/83, T 0612/09

**Catchword:**



**Beschwerdekammern**  
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Case Number: T 2154/14 - 3.3.04

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.04**  
**of 29 March 2017**

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**Decision under appeal:** **Decision of the Opposition Division of the  
European Patent Office posted on 1 September  
2014 revoking European patent No. 1115417  
pursuant to Article 101(3) (b) EPC.**

**Composition of the Board:**

**Chairwoman**            G. Alt  
**Members:**            R. Morawetz  
                             M. Blasi

## **Summary of Facts and Submissions**

- I. European patent No. 1 115 417, entitled "*Use of daptomycin*", was granted in respect of European patent application No. 99 949 913.0, which originated from international patent application PCT/US1999/022366, published as WO 00/018419. The patent claims the priority of US application 60/101,828 filed 25 September 1998 (hereinafter "P1") and US application 60/125,750 filed 24 March 1999 (hereinafter "P2").
- II. The patent has been opposed by opponents 1 and 2 under Article 100(a) EPC 1973 for lack of novelty (Article 54 EPC 1973) and lack of inventive step (Article 56 EPC 1973), and under Articles 100(b) and 100(c) EPC 1973. In addition, opponent 1 opposed the patent under Article 100(a) EPC 1973 for lack of patentability (Article 52(4) EPC 1973).
- III. The opposition division decided that both the main request and the auxiliary request then before it contravened Article 123(2) EPC and revoked the patent.
- IV. An appeal was lodged by the patent proprietor against this first decision of the opposition division.
- V. The board, in a composition different from the present one, decided in the first appeal proceedings (cf. decision T 612/09 of 11 April 2013) that, while the main request failed the requirements of Article 123(2) EPC, the auxiliary request (filed as second auxiliary request with the proprietor's letter of 10 October 2008) complied with the requirements of Article 123(2) EPC. The case was remitted to the opposition division for further prosecution.

VI. The opposition division decided that the subject-matter of claim 1 of the main request before it (which corresponds to the auxiliary request filed as second auxiliary request with the proprietor's letter of 10 October 2008) lacked an inventive step in view of the teaching of document D8 in combination with the disclosure of document D13 and/or document D1 (Article 56 EPC 1973) and that the subject-matter of claim 1 of the auxiliary request did not meet the requirements of Articles 84 and 123(2) EPC and revoked the patent anew.

VII. The appeal of the patent proprietor (hereinafter "the appellant") lies against this second decision of the opposition division. Opponent 1 and opponent 2 are the respondents in these proceedings (hereinafter "respondent I" and "respondent II" or "the respondents").

VIII. The following documents are referred to in this decision:

D1 Baltz R.H., in W.R. Strohl (Editor) *Biotechnology of Antibiotics*, Second Edition, Marcel Dekker, Inc., New York 1997, pages 415 to 435.

D8 Cubist Press release (1 March 1999).

D13 Oleson F.B. Jr. et al., *The Toxicologist* (March 1999), abstract 1520, page 322.

D26 *The Toxicologist* (March 1999), Abstracts of the 38th Annual Meeting, vol. 48, Supplement, extract, pages 1 to 4.

D28 Society of Toxicology, 38th Annual Meeting,  
14-18 March 1999, program, extract,  
pages 1 to 36.

- IX. In its statement of grounds of appeal the appellant maintained the claim requests underlying the decision under appeal as its sole claim requests.

Claim 1 of the main request reads:

"1. Use of daptomycin for the manufacture of a medicament for treating a bacterial infection in a human patient in need thereof, wherein a dose for said treating is 3 to 10 mg/kg of daptomycin, wherein said dose is repeatedly administered in a dosage interval of once every 24 hours."

Claim 1 of the auxiliary request reads:

"1. Use of daptomycin for the manufacture of a medicament for treating a bacterial infection in a human patient in need thereof, wherein a dose for said treating is 3 to 10 mg/kg of daptomycin but excluding 3 mg/kg, wherein said dose is repeatedly administered in a dosage interval of once every 24 hours."

- X. Among the objections raised by the respondents in their respective replies to the statement of grounds of appeal was that the subject-matter of claim 1 of the main request lacked inventive step in view of the combination of the teaching of document D1 with the disclosure of document D13 (see respondent I's reply to the statement of grounds of appeal point 3.16 and respondent II's reply to the statement of grounds of appeal page 10, third paragraph).

- XI. The board summoned the parties to oral proceedings and issued a communication pursuant to Article 15(1) RPBA.
- XII. Oral proceedings before the board took place on 28 and 29 March 2017. On the second day of the oral proceedings the appellant filed a new auxiliary request and withdrew its pending auxiliary request.

The sole claim of the new auxiliary request reads:

"1. Use of daptomycin for the manufacture of a medicament for treating a bacterial infection in a human patient in need thereof, wherein a dose for said treating is 4 or 6 mg/kg of daptomycin, wherein said dose is repeatedly administered in a dosage interval of once every 24 hours."

At the end of the oral proceedings the chairwoman announced the board's decision.

- XIII. The appellant's arguments relevant for the present decision may be summarised as follows:

*Main request*

*Priority (Article 87(1) EPC 1973)*

*Entitlement to priority from P1 - claim 1*

The range of 3 to 10 mg/kg daptomycin was disclosed in the priority application P1 because it was derivable from the explicitly disclosed range of 2 to 10 mg/kg daptomycin (see page 2, final paragraph). This was in line with the Enlarged Board of Appeal opinion G 2/98 (Reasons, point 8.4) and decision G 1/15 (Reasons, point 5.1.2).



P1 also provided a basis for the combination of the range of 3 to 10 mg/kg daptomycin with the dosage interval of once every 24 hours. The key message derivable from P1 read as a whole was that longer dosing intervals, i.e. 24 hours, were preferred. On page 2 under the heading "*Implications for Clinical Dosing*" the conclusion was drawn that "*longer intervals between doses*" will be beneficial because they "*will minimize the possibility of muscle toxicity in the clinical setting and may permit the use of higher doses than have been possible so far.*" The skilled person would therefore have seriously contemplated using as long an interval as possible, i.e. the 24-hour interval disclosed in the final paragraph on page 2 of P1.

*Entitlement to priority from P2 - claim 1*

Following the reasoning developed in decision T 201/83 and applied in decision T 612/09 that a specifically disclosed dosage value could be taken as the end point of a sub-range, provided that, for the skilled person, that value was recognisable as a singularity within or at the end of a range of possibilities, the broader range 2 to 10 mg/kg daptomycin recited in claim 2 of P2 could be amended to the sub-range of 3 to 10 mg/kg daptomycin based on the disclosure of the specific value 3 mg/kg daptomycin in claim 3 of P2.

Once-daily dosing was disclosed to be preferred in the description of P2, see the paragraph bridging pages 3 and 4 and lines 7 and 9 on page 4. Therefore, it could be combined with the dose range that resulted from a combination of claims 2 and 3.

Dependent claims were statements of preferred embodiments. The subject-matter of claim 4 could thus

also be combined with that of claims 2 and 3. The combination of the subject-matter of claims 2, 3 and 4 of P2 thus also provided a disclosure for the combination of the range of 3 to 10 mg/kg daptomycin with administration of once daily.

Claim 1 of P2 referred to a therapeutically effective amount, and dependent claim 2 defined that amount to include 3 mg/kg daptomycin. That this amount was also effective if administered every 24 hours was the direct teaching of claim 4. P2 thus disclosed that a dose of 3 mg/kg daptomycin was therapeutically effective if administered once daily.

*Document D13 - availability to the public*

The respondents had not established that document D13 was available to the public before the filing date of P2. Document D13 was an abstract, and there was no evidence that this abstract was disclosed at the Society of Toxicology (SOT) 1999 Annual Meeting or when it was subsequently published. The abstract was included on a page that referred to the SOT 1999 Annual Meeting, but this reference did not prove whether document D13 itself was published before or after 24 March 1999, the second priority date.

Documents D26 and D28 did not establish that document D13 was prior art or that its content had been disclosed at the SOT 1999 Annual Meeting. Nothing in document D26 indicated that the abstract was available before 24 March 1999. Page 4 of document D26 differed from document D13 in that the line at the bottom of the page which read "*Supplied by The British Library - 'The world's knowledge'*" was missing.

It had not been established that document D26 was an extract from the abstract volume referred to in document D28.

*Inventive step (Article 56 EPC 1973)*

*Closest prior art*

In selecting the closest prior art, a central consideration was that it had to be directed to the same purpose or effect as the invention. The claimed invention related to the treatment of bacterial infections in humans with daptomycin at doses which maintained efficacy and provided minimum toxicity (see also paragraph [0010] of the patent).

The opposition division had erred in taking document D8 to represent the closest prior art. Not document D8 but document D1 represented the closest prior art. It reviewed the clinical trials that had been carried out on daptomycin (see page 423, last paragraph to page 424, third paragraph) and discussed possible approaches for solving the muscle toxicity problem (see page 430, last paragraph). It related to the same purpose as the patent, i.e. the use of daptomycin to treat bacterial infections and the same effect, i.e. the problem of skeletal muscle toxicity. The disclosure in document D1 that 3 mg/kg daptomycin every 12 hours was shown to be effective was the closest prior art.

Although document D8 related to the same purpose as the invention, i.e. the use of daptomycin to treat bacterial infections, it did not show any concrete suitability for this purpose. It did not show that any of the treatments proposed were effective in treating bacterial infections and it did not relate to the same

effect as the patent, the problem of skeletal muscle toxicity. There was no mention of muscle toxicity anywhere in document D8. It was therefore more distant from the claimed invention than document D1.

*Technical problem and its solution*

The subject-matter of claim 1 differed from the dosage regimen disclosed in document D1 in the dosing frequency, every 24 hours, possibly in combination with the dose of daptomycin, 3 to 10 mg/kg. The technical effect associated with these differences was the treatment of bacterial infections in humans while avoiding muscle toxicity and - for daptomycin doses higher than 3 mg/kg - improved efficacy.

Example 4 of the patent showed that patients treated once daily with 6 mg/kg of daptomycin for 21 days experienced no muscular pain or weakness. The data provided in the patent in the context of the dog studies and the human studies allowed the conclusion that once-daily administration of daptomycin improved muscle toxicity, see also paragraph [0019] of the patent.

The problem to be solved could thus be formulated as the provision of an improved treatment compared with the treatment disclosed in document D1, one that avoided muscle toxicity and was capable of showing increased efficacy at higher doses.

*Obviousness*

The claimed solution was not obvious. First, document D1 taught away from the invention by suggesting that higher, more frequent dosing was

required for efficacy (see page 424, third full paragraph). Document D1 also taught that administration of higher daptomycin concentrations at more frequent dosing intervals was not considered to be a realistic option because of the known side effects in muscle (see page 424, first full paragraph). Second, document D1 proposed a solution different from the claimed one, namely the use of a daptomycin analog (see page 430, final paragraph).

There was no teaching in document D1 or anywhere else in the prior art to prolong the dosing interval.

Document D13 related to studies carried out in dogs, not humans, and it was silent on the possible reversibility of clinical skeletal muscle toxicity.

Nothing in document D13 suggested the claimed dosage regimen. The skilled person would not take once-daily administration without the dose (75 mg/kg) from document D13 and apply it to the dosage regimen disclosed in document D1.

Document D8 provided no technical data and no rationale for the clinical trials it disclosed.

*New auxiliary request*

The limitation to two specific doses, i.e. 4 or 6 mg/kg of daptomycin, was a simple amendment and the claim request should thus be admitted into the appeal proceedings. Although the opposition division had based its decision also on a combination of documents D1, D8 and D13, it had taken document D8, not document D1, as the closest prior art. Taking document D1 as the closest prior art had changed the analysis. The

combination of documents D1 and D13 had not been made prominently before on appeal and changed the respondents' case. A mere back-reference to an earlier submission, as in respondent I's reply to the statement of grounds of appeal, was not sufficient under Article 12(2) RPBA.

XIV. The respondents' arguments relevant for the present decision may be summarised as follows:

*Main request*

*Priority (Article 87(1) EPC 1973)*

*Entitlement to priority from P1 - claim 1*

The subject-matter of claim 1 was not directly and unambiguously derivable from P1.

P1 did not disclose the claimed range of 3 to 10 mg/kg daptomycin.

Nor did P1 disclose the combination of the claimed range of doses with a dosing interval of once every 24 hours. In P1 the range of 2 to 10 mg/kg daptomycin was disclosed in combination with a range of dosage intervals of between 12 and 24 hours. In terms of efficacy, P1 disclosed that larger doses should be administered less frequently as opposed to smaller doses.

There was a functional relationship between the dosing interval and the dose of daptomycin in terms of safety and efficacy. This functional relationship meant that the disclosure in P1 of a range of doses, together with a range of dosing intervals, was not a clear and

unambiguous disclosure that each specific combination of dose and interval within the two ranges would be a safe and effective treatment for a human patient. The doses and the frequency were not independent variables. The combination of the lower end of the dose range with the higher end of the dosage interval was thus not disclosed and therefore the dose range of 2 to 10 mg/kg daptomycin could not be combined with once every 24 hours.

P1 read as a whole did not provide a pointer to the dosage interval of once every 24 hours. Having looked at the dog data, P1 concluded that longer intervals, i.e. "once every 12 hours to 24 hours", minimise toxicity. This did not mean that 24 hours was preferred. Also the dosage regimen disclosed in P1 for patients combined doses of 2 to 10 mg/kg daptomycin with intervals between 12 and 24 hours.

*Entitlement to priority from P2 - claim 1*

The subject-matter of claim 1 was not entitled to priority from P2. The opposition division was not correct in finding that the reasoning of decision T 612/09 as regards the requirements of Article 123(2) EPC applied because the relevant passages were different in P2 and in the application as filed.

The combination of the subject-matter of claims 2 and 3 of P2 did not disclose the range of 3 to 10 mg/kg of daptomycin, but only 3 mg/kg daptomycin.

Claim 4 was dependent on claim 2 and not on claim 3. Claim 4 could thus not be combined with claim 2 and claims 2, 3 and 4 did not disclose directly and

unambiguously the combination of 3 to 10 mg/kg of daptomycin administered once every 24 hours.

The description of P2 put an emphasis on daily administration on pages 3 and 4 but P2 did not teach that 3 mg/kg daptomycin was effective if given once daily.

*Document D13 - availability to the public*

Document D26 was an extract from the abstract volume of *The Toxicologist* referred to in document D28. Page 4 of document D26 corresponded to document D13. Document D26 used the same page numbering (page 322) as document D13.

Document D28 was the program for the 38th Annual Meeting of the Society of Toxicology (SOT), held on 14 to 18 March 1999, i.e. prior to the filing date of P2, which is 24 March 1999. On page 6, document D28 provided evidence that document D13 had been made available to the public before 24 March 1999 because it was part of the abstract volume of *The Toxicologist* which the attendees got at the latest at the Annual Meeting.

Document D28 disclosed on page 152 the title and the authors of abstract No. 1520, which corresponded to abstract No. 1520 of documents D26 and D13.



*Inventive step (Article 56 EPC 1973)*

*Closest prior art*

The opposition division was correct in taking document D8 as the closest prior art. Document D8 had the same purpose as the claimed invention, namely the use of daptomycin to treat bacterial infections, and was structurally closer than document D1. Thus, it disclosed dosing regimens falling within the scope of the claimed regimen, namely 4 mg/kg and 6 mg/kg daptomycin every 24 hours. It also stated that daptomycin had already exhibited efficacy and a favourable side-effect profile in clinical trials that had been completed.

Document D1 was structurally further away from the claimed invention because it disclosed that 2 mg/kg daptomycin every 24 hours or 3 mg/kg daptomycin every 12 hours was effective but it was silent on 3 to 10 mg/kg daptomycin.

*Technical problem and its solution*

Example 4 of the patent provided no data on efficacy. The skilled person knew that daptomycin had a concentration-dependent bactericidal effect, so all that mattered was the peak concentration of daptomycin that occurred in the bloodstream after administration ( $C_{max}$ ). That a higher dose of daptomycin would be more efficacious thus followed from the common general knowledge but was not actually shown in the patent. But there was no reason to think that 3 mg/kg daptomycin administered every 24 hours was better than 3 mg/kg daptomycin administered every 12 hours in terms of efficacy as  $C_{max}$  was the same in both cases.

Example 4 did not focus on toxicity generally but only on skeletal muscle toxicity. The patent provided no data for 10 mg/kg daptomycin administered every 24 hours or for the entire claimed dosage regimen in terms of toxicity.

The problem to be solved was thus the provision of an alternative treatment compared with the treatment disclosed in document D1.

*Obviousness*

The subject-matter of claim 1 lacked inventive step even if document D1 was taken to represent the closest prior art.

Document D1 disclosed that the rate of bacterial killing by daptomycin was dose-dependent and that 2 mg/kg daptomycin given every 24 hours and 3 mg/kg daptomycin given every 12 hours were effective in humans. Document D1 however also disclosed that elevated doses of daptomycin might cause muscle toxicity.

Regardless of whether document D8 or document D1 was taken as the closest prior art, the skilled person concerned with muscle toxicity of daptomycin would have turned to document D13. This document reported that it had been found that toxicity was not related to  $C_{max}$  or to the total concentration of daptomycin in the bloodstream for 24 hours ( $AUC_{24h}$ ) and that the data suggested that the dosing interval had a greater influence on toxicity than did the dose itself.

Document D13 concluded that the results suggested that once-daily dosing could minimise daptomycin muscle toxicity, while optimising its antimicrobial effect.

Thus, document D13 gave the skilled person a reasonable expectation that a once-daily dosing regimen was safe with respect to skeletal muscle toxicity in humans.

Document D8 confirmed that once-daily dosing of daptomycin was the way forward.

The author of document D1 was not aware of the teaching of document D13 and therefore suggested other solutions, e.g. daptomycin analogs.

Daptomycin had been developed for use in humans, the skilled person reading document D13 was aware of this. The toxicity that was studied in document D13 was the one that was relevant to daptomycin's use in humans, see document D1. The authors of document D13 would not have studied dogs unless the results of the studies were to be considered relevant for humans. Document D13 concluded that "*once daily*" was safe and the skilled person understood that this applied to humans, human toxicity being the whole point of the study.

The skilled person would not use a dose of 75 mg/kg daptomycin in humans. He knew that daptomycin was a concentration-dependent antibiotic and that  $C_{\max}$  was relevant for efficacy of daptomycin in humans. The effective dose for humans was known from document D1 to be 3 mg/kg daptomycin. From document D13 he learned that toxicity was not dependent on  $C_{\max}$  or  $AUC_{24h}$  and that once-daily administration reduced toxicity.

*New auxiliary request*

The request had been filed at a very late stage of the appeal proceedings.

The opposition division had already decided that the subject-matter of claim 1 lacked inventive step over document D8 as the closest prior art in combination with the teaching of documents D1 and D13. If the change from "3 to 10 mg/kg of daptomycin" to "4 or 6 mg/kg of daptomycin" was, as submitted by the appellant, a simple amendment to address the combination of these documents, then this amendment could already have been filed before the opposition division - but it was not.

On appeal, the respondents had also argued lack of inventive step starting from document D1 as the closest prior art. The combination of document D1 and document D13 had been made in the written submissions (see respondent I's reply to the statement of grounds of appeal, point 3.16 which referred back to the submissions of 28 April 2014 and respondent II's reply to the statement of grounds of appeal, page 10, third paragraph). There was no new case made by the respondents. The appellant had started from document D1 as the closest prior art and should have prepared its fall-back positions sooner.

It was moreover *prima facie* unlikely that the amendment could establish inventive step given that document D8 disclosed the exact same doses of daptomycin as claimed now.

The new auxiliary request should not be admitted into the proceedings because this would be unfair on the respondents.

- XV. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request underlying the decision under appeal, or alternatively, on the basis of the claim filed as auxiliary request at the oral proceedings before the board.

The respondents requested that the appeal be dismissed.

## **Reasons for the Decision**

### *Main request*

### *Priority (Article 87(1) EPC 1973)*

### *Entitlement to priority from P1 - claim 1*

1. Claim 1 is drawn up in the so-called Swiss-type format and concerns a dosage regimen - 3 to 10 mg/kg once every 24 hours - for treating a bacterial infection in a human patient with the antibiotic daptomycin (see section IX). The opposition division held that the dose range "3 to 10 mg/kg" was not directly and unambiguously derivable from the first priority application, P1 (see decision under appeal, point 3.2).
2. According to established case law, the requirement for validly claiming priority of "*the same invention*", referred to in Article 87(1) EPC 1973, means that priority of a previous application in respect of a claim in a European patent application in accordance

with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole (cf. opinion G 2/98 of the Enlarged Board of Appeal, OJ EPO 2001, 413, headnote).

3. The appellant submitted that (i) the range of 3 to 10 mg/kg daptomycin was derivable from the explicitly disclosed range of 2 to 10 mg/kg daptomycin in P1, in line with opinion G 2/98 (*supra*, see Reasons, point 8.4) and further confirmed by decision G 1/15 of the Enlarged Board of Appeal (see Reasons, point 5.1.2). The appellant further submitted that (ii) P1 also provided a basis for the combination of the range of 3 to 10 mg/kg daptomycin with the dosage interval of once every 24 hours.
4. In the following the board will first concentrate on the second part of appellant's argument.
5. P1 reports on studies carried out in dogs to understand the factors governing the muscle toxicity produced by daptomycin. P1 concludes from the dog studies that the frequency of administration is an important variable in determining the muscle toxicity of daptomycin and that, rather than being strictly related to the dose level, the degree of muscle damage appears to be related to the time between treatments (see page 2, second paragraph).
6. As regards the implications of these findings for clinical dosing P1 states that "*the findings described above suggest that longer intervals between doses of daptomycin (i.e. once every 12 hours to 24 hours) will minimize the possibility of muscle toxicity in the*

*clinical setting and may permit the use of higher doses than have been possible so far"* (see page 2, third paragraph).

7. P1 also discloses that in terms of clinical efficacy, which appears to be related to the peak serum level attained, larger doses of daptomycin should be administered less frequently as opposed to smaller doses more frequently (see page 2, third paragraph).
8. Therefore, P1 discloses to the skilled person that there is a functional relationship between the dose of daptomycin and the dosing interval in terms of safety as regards the problem of skeletal muscle toxicity caused by the antibiotic (see points 5 and 6) and in terms of efficacy in treating the bacterial infection (see point 7). It follows that in a dosage regimen the dose of daptomycin and the frequency of its administration are not independent variables but are functionally linked.
9. As regards administration to humans, P1 discloses that *"daptomycin is administered to a patient in need of such treatment at a dose of between 2 and 10 mg/kg and subsequently, re-administering that same dose at intervals between 12 and 24 hours"* (see page 2, fourth paragraph).
10. To the skilled person, aware of the functional relationship between the dose of daptomycin and the dosing interval, the disclosed combination of the dose range of 2 to 10 mg/kg daptomycin with a range of dosage intervals of between 12 and 24 hours therefore does not clearly and unambiguously disclose that the lower end of the dose range, e.g. 2 mg/kg of daptomycin, is not only safe but also efficacious to

treat a bacterial infection if only administered once every 24 hours. Accordingly, the combination of the dose range of 2 to 10 mg/kg daptomycin with the dosage interval of once every 24 hours is not directly and unambiguously derivable from P1.

11. The appellant submitted that longer administration was highlighted in P1 and that P1 thus provided a pointer to administration of daptomycin once every 24 hours in humans.
12. The board is not persuaded by this line of argument. P1 explicitly discloses longer intervals to be "*once every 12 hours to 24 hours*", and thus does not disclose an interval of 24 hours only (see point 6). Therefore, P1 provides no pointer to a dosage interval of 24 hours and thus also not to the combination of the dose range of 2 to 10 mg/kg daptomycin with the dosage interval of once every 24 hours.
13. The board concludes from the above that there is no clear and unambiguous disclosure in P1 of the combination of the dose range of 2 to 10 mg/kg of daptomycin with a dosage interval of "*once every 24 hours*" and that for that reason alone the subject-matter of claim 1 is not entitled to priority from P1.
14. Therefore, it need not be decided whether or not the first part of appellant's argument, i.e. that the dose range of 3 to 10 mg/kg of daptomycin is disclosed in P1, is correct.

*Entitlement to priority from P2 - claim 1*

15. The opposition division decided that page 5, lines 1 to 2, of P2 disclosed the subject-matter of claim 1 and



that the effective date for claim 1 was thus the filing date of P2 (see decision under appeal, points 3.3 and 3.4). The respondents contested this part of the decision. In the board's view, the question whether or not page 5, lines 1 to 2, of P2 discloses the claimed subject-matter can be left open if there are other passages in P2 which do disclose the subject-matter of claim 1.

16. Claim 1 of P2 discloses *"administering to a patient in need thereof a therapeutically effective amount of daptomycin in a dose of 2 to 75 mg/kg of daptomycin, wherein the daptomycin is administered once every 12 to 24 hours."* Dependent claim 2 defines the dose to be *"2 to 10 mg/kg"* while claim 3, which depends on claim 2, defines the dose to be *"3, 4, 5, 6, 7, 8 or 9 mg/kg"*. Claim 4 depends on claim 2 and defines that *"daptomycin is administered once every 24 hours"*.
17. In the board's opinion, the skilled person recognises the value 3 mg/kg of daptomycin in claim 3 as a singularity within or at the end of a range of possibilities, which value may therefore mark an end-point for a particular sub-range (cf. decision T 201/83, OJ EPO 1984, 481, Reasons, points 8 and 9). Following the reasoning developed in decision T 201/83 (*supra*, Reasons, point 12) the broader range of 2 to 10 mg/kg daptomycin recited in claim 2 of P2 in combination with the disclosure of the specific value 3 mg/kg in claim 3 of P2 thus discloses directly and unambiguously the sub-range of 3 to 10 mg/kg daptomycin.
18. From the description of P2 the skilled person learns that the data obtained in two dog studies *"suggest that dosing interval had a greater influence on muscle*

*toxicity than did dose itself*" (see page 3, lines 24 to 29), and further that *"studies in animal efficacy models have demonstrated that effectiveness of daptomycin is optimized by once-daily dosing"* (sentence bridging pages 3 and 4) and that *"these results suggest that once-daily dosing can minimize daptomycin muscle toxicity, while optimizing its antimicrobial efficacy"* (see page 4, lines 2 to 4). In the board's view, the description of P2 thus puts a clear emphasis on once-daily dosing of daptomycin. Also according to claim 4 of P2, which is dependent on claim 2, daptomycin *"is administered once every 24 hours"*. The combination of the range of 3 to 10 mg/kg daptomycin with the specific dosage interval of once every 24 hours is thus directly and unambiguously derivable from the description of P2 and is further confirmed by dependent claim 4 of P2 which provides a clear emphasis on the 24-hour dosage interval.

19. The respondents also submitted that P2 did not disclose that a dose of 3 mg/kg daptomycin was also therapeutically effective if given once daily.
20. However, claim 1 relates to a therapeutically effective amount of daptomycin which includes also 3 mg/kg. Dependent claim 2 narrows the dose to 2 to 10 mg/kg of daptomycin and according to claim 4, which depends on claim 2, administration is once every 24 hours. Accordingly, P2 discloses that a dose of 3 mg/kg daptomycin is therapeutically effective if given once daily.

21. The board concludes from the above that the subject-matter of claim 1 is entitled to priority from P2 when read as a whole, in particular in combination with the subject-matter as defined in claims 1 to 4.

*Conclusion as regards entitlement to priority - claim 1*

22. The subject-matter of claim 1 is not entitled to priority from P1 but is entitled to priority from P2. The effective date of the subject-matter of claim 1 of the main request is thus the filing date of P2, i.e. 24 March 1999.

*Document D13 - availability to the public*

23. Document D13 consists of one page of abstracts, including abstract No. 1520 entitled "*Once-daily dosing decreases toxicity of daptomycin*". The opposition division considered that, for the subject-matter of claim 1, the effective date of which was the filing date of P2, document D13 belonged to the state of the art within the meaning of Article 54(2) EPC 1973 (see decision under appeal, point 4.2). The appellant disputed that document D13 or its content was available to the public before 24 March 1999.
24. Document D13 does not bear a publication date or date stamp. At the bottom of the page the page number, "322", is indicated followed by "*SOT 1999 Annual Meeting*". At the very bottom of the document, the statement "*Supplied by The British Library - 'The world's knowledge'*" is printed. From document D13 itself it is thus not apparent whether or not it was published before 24 March 1999.

25. The respondents relied on two further documents, D26 and D28, to establish the date on which the content of document D13 became available to the public. Document D26, an extract from a supplement of *The Toxicologist* (see pages 1 and 2), discloses on page 3 that "*this issue of The Toxicologist is devoted to the abstracts of the presentations for the symposium, platform, poster/discussion, workshop, roundtable, and poster sessions of the 38<sup>th</sup> Annual Meeting of the Society of Toxicology, held at the Ernest N. Morial Convention Center, New Orleans, Louisiana, March 14-18, 1999*" (see first paragraph) and that "*the abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence*" (fourth paragraph). The fourth page of document D26 bears the page number "322" and is identical to document D13, with the sole difference that the statement at the bottom of the page which reads "*Supplied by The British Library - 'The world's knowledge'*" is absent.
26. In the board's view, document D26 establishes that the content of document D13 formed part of the abstracts volume of *The Toxicologist*. The board has no reason to doubt that page 4 of document D26 belongs to the abstracts volume of *The Toxicologist*: "SOT" is obviously the abbreviation for "Society of Toxicology" (see also e.g. page 10 of document D28) and a clear reference to the annual meeting in 1999 is given on page 4 of document D26 itself. That document D13 contains the additional statement "*Supplied by The British Library...*" at the very bottom is not in contradiction to page 4 of document D26 since the appearance of document D13 suggests that the latter is a photocopy of a paper document with the additional statement added to the copied original. That

document D13 was supplied by the British Library while document D26 was not has no bearing on the issue to be decided, namely the public availability of the content of document D13.

27. Document D28, an extract of the Program of the 38th Annual Meeting of the Society of Toxicology held on 14 to 18 March 1999 (see page 1) discloses on the page bearing page number 6 (page 10 of the document) under the heading "*Receipt of the Program and The Toxicologist*" that: "*1. SOT members in the U.S. and Canada will receive the Program and The Toxicologist (abstracts volume) prior to the meeting as will U.S. and Canadian members who pre-register by January 11, 1999. 2. SOT members and non-member pre-registrants outside the US and Canada, as well as non-members in the U.S. who register after January 11, will receive the Program and The Toxicologist at the registration desk on-site(...) Note: Please bring your copy of the Program and The Toxicologist with you to the meeting.*"
28. In the board's view, document D28 thus establishes when the abstracts volume of *The Toxicologist* and thus also the content of document D13 became available to the public.
29. The appellant submitted that no link between document D28 and document D26 had been established.
30. However, the board notes that document D28 contains under the heading "*Poster Sessions*" *inter alia* a reference to abstract Nos. 1500-1540 (see page numbered 20/page 24 of D28, right-hand column). The title and the authors of abstract No. 1520 disclosed in document D28 (see page 36 of D28, in the middle of the right-

hand column) correspond to the title and authors given on page 4 of document D26 for abstract No. 1520. The board is thus convinced that document D26 is an extract from the abstract volume of *The Toxicologist* referred to in document D28.

31. Based on the evidence presented to it, the board thus concludes that the content of document D13 became available to the public at the latest as of the first day of the 1999 Annual Meeting of the Society of Toxicology, i.e. 14 March 1999, in the form of a written abstract contained within the abstracts volume of *The Toxicologist* (see points 25 and 26) handed out at the registration desk to the attendees of the 1999 Annual Meeting (see points 27 and 28). Its content therefore forms part of the state of the art within the meaning of Article 54(2) EPC 1973 for the subject-matter of claim 1.

*Inventive step (Article 56 EPC 1973)*

32. The opposition division had held that document D8 represented the closest prior art for the claimed invention and that the claimed subject-matter was obvious in view of document D8 in combination with the teaching of document D13 and/or document D1 (see decision under appeal, reasons, points 6.1 to 6.4).
33. On appeal, the parties disagreed on which document represented the closest prior art. While the appellant submitted that document D1 was the closest prior art, the respondents maintained that document D8 represented the closest prior art.
34. In accordance with established jurisprudence, the closest prior art for assessing inventive step is

normally a prior-art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016, section I.D.3.1).

35. The purpose of the claimed invention is the treatment of a bacterial infection in a human patient. According to paragraph [0010] of the patent the invention addresses the problem of skeletal muscle toxicity at high doses of daptomycin and provides for the use of the antibiotic in a manner that minimises skeletal muscle toxicity while simultaneously maintaining a sufficient efficacy level.
  
36. Document D1 discloses that "*daptomycin is bactericidal in Gram-positive pathogens, including enterococci (...), and the rate of killing is dose-dependent*" (see page 420, fourth paragraph, line 7). Document D1 also reviews the clinical trials that have been carried out on daptomycin in human patients (see page 423, last paragraph, to page 424, third paragraph). It discloses that "*at a dose of 2 mg/kg every 24 hr, daptomycin was shown to be effective in treating a variety of Gram-positive infections*" (see page 424, lines 5 to 6) and that "*in another study, daptomycin given at a dose of 3 mg/kg every 12 hr was shown to be effective in treating Gram-positive bacteremias and endocarditis caused by Gram-positive pathogens (including E. faecalis) other than S. aureus*" (ibid., lines 6 to 9) but also that "*the occasional adverse effects noted at a dose of 3 mg/kg every 12 hr seemed to preclude raising the dose further, and clinical trials were stopped*" (ibid., lines 14 to 15). On page 430,

penultimate paragraph, document D1 recapitulates that *"daptomycin is a potent antibiotic that is bactericidal for all of the most important Gram-positive pathogens"* and that *"elevated doses of daptomycin suggested that it may cause muscle toxicity in some patients, and so the clinical trials were stopped"*.

37. Document D8, a press release, discloses that *"Cubist Pharmaceutical Inc has initiated clinical trials for intravenous daptomycin"* (abstract, lines 1 to 2). Daptomycin is said to have exhibited *"a favourable side effect profile in clinical trials completed to date and will be administered as a once a day therapy"* (ibid., lines 4 to 6). In a phase 3 trial patients *"will receive 4 mg/kg intravenously once every 24 hours for 14 days"* (ibid., lines 8 to 11) and in an open-label phase 2 trial *"daptomycin dosage levels of 4 mg/kg and 6 mg/kg administered intravenously once every 24 hours will be compared to the 3 mg/kg every 12 hour regimen used in a previous Phase 2 study"* (ibid., lines 11 to 15).
38. Thus, while document D1 reviews the results of completed clinical trials in humans which had shown that the treatment of bacterial infections with daptomycin was effective, document D8 does not report on the outcome of the clinical studies it describes.
39. Therefore, the board takes the view that document D1 represents the more promising springboard than document D8, and accepts that the clinical study reported in document D1, wherein 3 mg/kg daptomycin administered every 12 hours was used to treat bacterial



infections, represents the closest state of the art for the purpose of the assessment of inventive step of the subject-matter of claim 1.

*Technical problem and its solution*

40. The subject-matter of claim 1 differs from the clinical study reported in document D1 in the combination of a dosing range of daptomycin, 3 to 10 mg/kg, with a particular dosing frequency, every 24 hours.
41. According to the appellant the technical effect associated with this difference is the treatment of bacterial infections in humans with an improvement in two aspects, efficacy at higher doses of daptomycin and avoidance of muscle toxicity. The appellant submitted that the problem to be solved could thus be formulated as the provision of an improved treatment for bacterial infections compared with the treatment disclosed in document D1, namely one that avoided muscle toxicity and was capable of showing increased efficacy at higher doses.
42. The respondents disputed that the problem to be solved could indeed be formulated as the provision of an improved treatment. First, an increased efficacy would be expected based on the prior art and could thus not be relied on for the formulation of the problem. Second, the patent provided data as regards the absence of adverse skeletal muscle effects in humans only for doses of 4 mg/kg and 6 mg/kg daptomycin administered every 24 hours, but not for higher doses of daptomycin.
43. The board considers that the respondents' argument as regards efficacy appears to go to obviousness ("would be expected"), but at the same time concedes that a

dose of daptomycin that is higher than the 3 mg/kg of daptomycin disclosed in document D1 would indeed be expected to be more efficacious (see also point 36 above).

As to the respondents' argument concerning the lack of evidence for the absence of muscle toxicity over the whole range claimed, the board accepts that the dog studies (see examples 1 to 3) and the human studies (see example 4) reported in the patent together credibly show that administration of daptomycin every 24 hours minimises skeletal muscle toxicity. The board thus also accepts that the problem to be solved is as formulated by the appellant.

#### *Obviousness*

44. The question which remains to be answered is whether the skilled person, aware of the teaching of document D1 and faced with the technical problem, would have modified the teaching of the closest prior art document D1 so as to arrive at the claimed invention in an obvious manner.
45. One embodiment of the invention as claimed is the administration of daptomycin at a dosage regimen of 3 mg/kg once every 24 hours. It is this embodiment which will be considered in the following.
46. As set out above (see point 36), document D1 discloses that daptomycin's bactericidal effect is dose-dependent, that 2 mg/kg given every 24 hours is effective as is 3 mg/kg given every 12 hours but also that some patients experienced adverse effects at 3 mg/kg given every 12 hours and that clinical trials were stopped because results at elevated doses of

daptomycin suggested that it may cause muscle toxicity in some patients.

47. In the board's view, the skilled person starting from a dosage regimen wherein 3 mg/kg daptomycin is administered every 12 hours and looking for a dosage regimen which while maintaining the efficacy of daptomycin reduces its toxicity (see the problem formulated in point 41 above) would have turned to document D13.

This document discloses that skeletal muscle has been identified as the target organ of daptomycin toxicity and reports on two studies conducted in dogs to investigate the potential effects of dose fractionation on toxicity. It reports that it has been found that toxicity was not related to the peak concentration of daptomycin that occurs in the bloodstream after administration ( $C_{max}$ ) or to the total concentration of daptomycin in the bloodstream for 24 hours ( $AUC_{24h}$ ) and that the data suggested that the dosing interval had a greater influence on toxicity than did the dose itself. It was hypothesised that once-daily administration of daptomycin would lead to lower toxicity because it would allow greater time between doses for repair of subclinical muscle damage associated with daptomycin. Further it also discloses that studies in animal efficacy models have demonstrated that effectiveness of daptomycin is optimised by once-daily dosing since  $C_{max}$  was found to be the key pharmacokinetic parameter associated with eradication of infection.

Document D13 concludes that the results suggested that once-daily dosing could minimise daptomycin muscle toxicity, while optimising its antimicrobial efficacy.

48. In the board's view, document D13 thus gives the skilled person a reasonable expectation that a once-daily dosing regimen of daptomycin is safe with respect to skeletal muscle toxicity, also in humans (see also point 55 below).
49. As set out above (see point 37), document D8 discloses that clinical trials have been initiated in which 4 or 6 mg/kg of daptomycin will be given once every 24 hours to patients. In the board's view, the disclosure of document D8 thus would reassure the skilled person that once-daily dosing of daptomycin in humans is the way forward.
50. As a first line of argument the appellant submitted that document D1 taught away from the invention by suggesting that higher, more frequent dosing was required for efficacy (see page 424, third full paragraph), but that this was not considered to be a realistic option because of the known side effects in muscle (see page 424, first full paragraph).
51. The appellant's argument implies that the skilled person would take from document D1 the suggestion of an alternative that he would consider so promising that he would abandon the teaching from the combination of documents D1 and D13. The board is not persuaded however that this is what the skilled person would do since document D1 itself also discloses that the suggested higher and more frequent dosing was not an option.

52. The appellant further submitted that document D1 proposed a solution different from the claimed one, namely the use of a daptomycin analog (see page 430, final paragraph).
53. The board notes that document D1 was published in 1997. The content of document D13 was thus not available at the time when document D1 was written. Thus it does not help the appellant's case that the author of document D1 - unaware of the teaching of document D13 - suggested other solutions, e.g. daptomycin analogs. At the effective date of the claim under consideration the skilled person was aware of the teaching of document D13 and would have considered that once-daily administration of daptomycin would avoid muscle toxicity (see point 47 above).
54. The appellant also disputed that the skilled person would even consider the teaching of document D13 as it reported on dog studies and not on human clinical trials. Furthermore, the skilled person would not separate the two aspects of the dosage regimen disclosed in document D13, i.e. once-daily dosing at a dose of 75 mg/kg daptomycin.
55. The board is not persuaded by these arguments either. As to the first argument, daptomycin has been developed for use in humans (see e.g. document D1, page 423, third paragraph, to page 424, fourth paragraph) and the skilled person reading document D13 is aware of this. Moreover, the kind of toxicity that is studied in document D13 is the one that is relevant to daptomycin's use in humans - this toxicity is already mentioned in document D1 (see page 430, third paragraph). It is thus, first, very unlikely that the authors of document D13 would have studied dogs unless

the results thus obtained were relevant for humans. Second, when document D13 concludes that "once-daily" is safe, the skilled person understands that this statement applies primarily to humans, since to gain more insight into the use of daptomycin in humans was the whole point of the study in dogs. In this context the board considers that it would not have escaped the skilled person that the dog studies in document D13 were carried out by the same company that had initiated clinical trials in humans which involved once-daily administration of daptomycin, see document D8.

56. As to the second argument, document D13 makes it clear that different parameters are responsible for toxicity and efficacy of daptomycin. Thus, while muscle toxicity did not appear to be directly related to  $C_{max}$ ,  $C_{max}$  was the key pharmacokinetic parameter associated with eradication of infection (see document D13, abstract). From document D1 the skilled person knows that a dose of 3 mg/kg daptomycin is effective in humans in treating Gram-positive bacteremias (see page 424, second paragraph). In the board's view, the skilled person would therefore not use the dose of 75 mg/kg daptomycin disclosed in document D13 for dogs but a dose of 3 mg/kg daptomycin.
57. The board concludes from the above that the skilled person would take once-daily administration from document D13 and apply it to the dose of daptomycin known to be efficacious in humans from document D1, 3 mg/kg, and thus arrive in an obvious manner at a dosage regimen, 3 mg/kg once every 24 hours, falling within the scope of claim 1. Consequently, the skilled person would have arrived at this embodiment of claim 1 in an obvious manner.

58. Therefore, the subject-matter of claim 1 as a whole must be considered to fail to meet the requirements of Article 56 EPC 1973.

*New auxiliary request*

*Admission into the appeal proceedings*

59. Claim 1 of the new auxiliary request differed from claim 1 of the main request in that the dose was now limited to 4 or 6 mg/kg of daptomycin (see section XII). The new auxiliary request amounted to an amendment to the appellant's case and its admission was thus at the board's discretion (Article 13 RPBA).

60. This claim request was filed on the second day of the oral proceedings after the board had given its opinion on inventive step of the subject-matter of claim 1 of the main request.

61. The appellant submitted that taking document D1 instead of document D8 as the closest prior art changed the inventive step analysis and that the combination of documents D1 and D13 had not been made prominently on appeal before. The mere back-reference in respondent I's reply to the statement of grounds of appeal to its earlier submissions as regards lack of inventive step was not sufficient under Article 12(2) RPBA. The new auxiliary request was a simple amendment in reaction to the board's opinion and should therefore be admitted into the appeal proceedings.

62. However, as already noted before, the opposition division had held that the subject-matter of claim 1 of the main request lacked inventive step over document D8

as the closest prior art in combination with the teaching of documents D13 and/or D1 (see point 32 above), i.e. the same three documents considered during these appeal proceedings in the context of inventive step right from the beginning.

63. Moreover, the line of reasoning starting from document D1 as closest prior art was the appellant's own case. And, as regards document D13, the respondents merely maintained that regardless of whether document D1 or document D8 was taken as the closest prior art, document D13 rendered once-daily administration of daptomycin obvious for the avoidance of muscle toxicity.
  
64. The board also considered that the line of argument relying on a combination of documents D1 and D13 could not be perceived as being hidden in the respondents' submissions or as being presented in a manner that it could be expected not to be taken into account by the board. Firstly, in the present case, the back-reference to submissions made during the proceedings before the opposition division was sufficient under Article 12(2) RPBA since (i) the relevant passages in the earlier submission were specifically identified, (ii) the line of argument was not contradicted by the decision of the opposition division, which was based on a different line of argumentation, and (iii) the subject-matter concerned was unchanged. Moreover, respondent II had mentioned the combination of documents D1 and D13 explicitly in its reply to the statement of grounds of appeal.



65. The board further noted that the appellant's main defense in relation to document D13 up to that point had been to argue that the document was not prior art.
66. In view of the above mentioned considerations the board concluded that there was no change in the case, certainly not one that qualified as an unforeseeable development in the proceedings. Moreover, that a board in *inter partes* proceedings finds at oral proceedings against a party is also not unexpected. Thus, filing of the amendment on the second day of the oral proceedings after the board had given its opinion on inventive step of the subject-matter of claim 1 of the main request could not be justified by the circumstances of the case.
67. And, furthermore, as regards the submission that the amendment was simple the board considers that, while the amendment as such might have been simple in the sense that it was easily understandable what the amendment was, in terms of lines of arguments to be considered, the consequences might not have been simple.
68. Finally, it was also not immediately apparent to the board that the new claim request was clearly and obviously allowable as document D8 already disclosed the administration of 4 or 6 mg/kg of daptomycin once daily in humans (see point 37).
69. Therefore, the board decided not to admit the new auxiliary request into the appeal proceedings (Article 13(1) and (3) RPBA).

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated