Neutral Citation Number: 2016-EWCH 1285(PAT)

Case No: HP-2014-000037

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Rolls Building
Fetter Lane
London EC4A 1NL

Date: Friday 10th June 2016

Before :

THE HON MR JUSTICE HENRY CARR

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Between :

Hospira UK Limited	**Claimant**
- and -	
Cubist Pharmaceuticals LLC	**Defendant**

- -
- -

Richard Meade QC and Isabel Jamal (instructed by **Taylor Wessing LLP**) for the **Claimant**
Andrew Waugh QC, Thomas Hinchliffe QC and Stuart Baran (instructed by **Carpmaels & Ransford LLP**) for the **Defendant**

Hearing dates: 21, 22, 25-29 April, 3, 5 and 6 May 2016

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Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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MR JUSTICE HENRY CARR

Mr Justice Henry Carr:

Introduction

1. The Claimant ("Hospira") seeks revocation of three patents ("the Patents") owned by the Defendant ("Cubist"), namely:

   i) EP (UK) 1,115,417 ("the 417 Patent");

   ii) EP (UK) 1,252,179 ("the 179 Patent"); and

   iii) EP (UK) 2,264,047 ("the 047 Patent").

2. All three patents concern the antibiotic daptomycin, which was originally discovered by Eli Lilly ("Lilly") in the 1980s. Daptomycin is a lipopeptide, and lipopeptides are molecules consisting of a lipid (a naturally occurring molecule such as a fat) connected to a peptide (a short chain of amino acids).

3. Cubist has made an unconditional application to amend the 417 Patent. References to the claims of the 417 Patent in this judgment are to the proposed amended form. The 417 Patent claims a dosage regimen for daptomycin of between 3-10 mg/kg administered once every 24 hours, for treating a bacterial infection. It has a first claimed priority date of 25 September 1998 and a second claimed priority date of 24 March 1999. The 417 Patent was filed on 24 September 1999. The 179 and 047 Patents concern purification processes for daptomycin (collectively "the Purity Patents"). They rely upon the same priority documents and their earliest claimed priority date is 20 January 2000.

4. The validity trial of all three patents was heard at the same time. This did not prove easy, either for the parties' legal representatives or for the court. The 417 Patent raised different issues and involved evidence from different experts to the Purity Patents. It would have been preferable to hear the trial of the 417 Patent first, followed shortly afterwards by the trial of the Purity Patents. Generally speaking, three patents with different subject matter are likely to prove too many for a single trial.

5. To date, none of the Patents has enjoyed a happy life. The US equivalent of the 417 Patent was held to be anticipated by and obvious over prior art relied on in these proceedings. US patents with common features to the Purity Patents (although not identical claims) were also held to be invalid over prior art relied on in these proceedings. Those decisions were affirmed on appeal. The Opposition Division of the EPO held that the 417 Patent was not entitled to its first priority date and was invalid for lack of inventive step. The decision of the Opposition Division is under appeal to the Technical Board of Appeal. However, I have heard different evidence and different arguments, and in respect of the US judgments, I am applying a different system of law. Other than passages to which I expressly refer, I have not relied on those decisions.

The issues

The 417 Patent

6. The following grounds of invalidity are relied upon by Hospira:

i) That the 417 Patent is not entitled to either of its claimed priority dates. Cubist accepts that if the 417 Patent is not entitled to either its first or second claimed priority dates, then it is invalid.

ii) That, as a result of non-entitlement to the first priority date, the 417 Patent is anticipated or rendered obvious by a Press Release published on 1 March 1999 ("the Cubist Press Release").

iii) Irrespective of the priority attacks, that Woodworth et al., *Single-Dose Pharmacokinetics and Antibacterial Activity of Daptomycin, a New Lipopeptide Antibiotic, in Healthy Volunteers*, Antimicrobial Agents and Chemotherapy (1992) ("Woodworth") anticipates the 417 Patent or deprives it of inventive step.

iv) That the claims as proposed to be amended add matter over the application as filed and claim 2 as proposed to be amended lacks clarity.

v) That the claims of the 417 Patent are not enabled across their full width. This is advanced as a squeeze with the attacks based on the prior art.

The 179 Patent

7. The following grounds of invalidity are relied upon by Hospira:

i) That the 179 Patent lacks inventive step over US 4,874,843 ("US 843").

ii) That the 179 Patent lacks inventive step over the common general knowledge alone and/or is a non-inventive collocation of known purification steps.

iii) That the claims of the 179 Patent add matter over the application as filed.

iv) That the claims of the 179 Patent are not enabled across their full width. Again, this is relied on as a squeeze with the prior art, in that it is alleged that the claims are not enabled insofar as they cover methods which do not use the method described in US 843.

v) That the same objections to validity apply to the conditional amendments proposed by Cubist.

The 047 Patent

8. Hospira alleges that the 047 Patent lacks inventive step over Lin & Jiang, *Recovery and purification of the lipopeptide biosurfactant of Bacillus subtilis by ultrafiltration*, Biotechnology Techniques (1997) ("Lin & Jiang"). At the start of the trial, Hospira also alleged that the 047 Patent was obvious over common general knowledge alone, but this was not pursued during closing speeches.

All Patents

9. As well as the patent-specific grounds of invalidity referred to above, Hospira relies on a further insufficiency attack which it alleges has application to all the Patents. This relates to the definition of "daptomycin" in the Patents. Hospira submits that the

Patents describe daptomycin as a) being produced by fermentation and b) having a particular stereochemistry, but that the two are inconsistent with each other, rendering the description incomprehensible and impossible to perform.

The 417 Patent

The witnesses in respect of the 417 Patent

Dr Ebert

10. Hospira's expert on the 417 Patent was Dr Steven Ebert. Dr Ebert is a clinical professor of pharmacy at the University of Wisconsin and clinical manager of infectious diseases at the Department of Pharmacy at Meriter Hospital in Wisconsin. His principal field of expertise is in developing and designing antibiotic dosing regimens. In the late 1980s Dr Ebert was involved in a dose-efficacy study of daptomycin against methicillin sensitive and methicillin resistant staphylococcus in a mouse-thigh model. He gave evidence for Hospira in the US proceedings.

11. Cubist criticises Dr Ebert's evidence. First, it alleges that he lacked the necessary qualifications and expertise to give evidence about the dosing regimen of the 417 Patent, in that he did not have experience with human clinical trials. I do not accept that this meant that Dr Ebert was unable to assist the court in respect of the subject matter of the 417 Patent. On the contrary, he had experience of pharmacokinetic and pharmacodynamic studies in animal models, including with daptomycin. He had experience of advising clinicians on dosing regimens and at the Meriter Hospital his role as a pharmacist required him to approve or reject antibiotic prescriptions ordered by physicians. He had extensive experience of teaching in the areas of infectious diseases, pharmacotherapy, antibiotic pharmacology and clinical pharmacokinetics. In my judgment he was well qualified to give expert evidence in relation to the 417 Patent, and was measured and fair during his cross-examination.

12. Secondly, Cubist criticises Dr Ebert for not dealing in his first report with the clinical trials that Lilly carried out on daptomycin in the early 1990s and the knowledge of the skilled team at the priority date about why those clinical trials were abandoned. Cubist alleges that he ought to have referred to a number of papers published between 1992 and 1998 which made reference to abandonment of those trials. I do not accept this criticism of Dr Ebert. He explained at [4.54] and [8.5]-[8.6] of his first report the information that he considered the skilled person would have found out about Lilly's clinical trials at the priority date. Furthermore, certain papers that Dr Ebert was criticised for omitting from his first report were also not referred to in the first report of Dr Harding, the expert witness for Cubist.

13. Thirdly, Dr Ebert was criticised for his evidence that it was common general knowledge at the priority date that the post antibiotic effect ("PAE") of daptomycin was likely to be greater than six hours in humans. Cubist submits that this evidence was partial, in that it ignored evidence from the Bush and Hanberger papers (referred to below) that there were a range of possible values for the PAE of daptomycin, most of which were substantially below a value of six hours. I do not accept this criticism of Dr Ebert. He exhibited the Bush and Hanberger papers and set out the relevant data. The fact that his opinion was contrary to Cubist's case does not mean that he was biased.

14. Fourthly, Dr Ebert was criticised for his reliance upon the dosing regimen for aminoglycosides in support of his opinion that once-daily dosing was obvious for daptomycin. It is suggested that this was a matter of controversy at the priority date, and that Dr Ebert had unfairly presented only one side of the picture. I reject this criticism of his evidence. As explained in more detail below, I consider that once-daily dosing as an option for aminoglycosides was well established at the priority date and Dr Ebert was entitled to refer to this in support of his conclusions.

Dr Harding

15. Cubist's expert on the 417 Patent was Dr Ian Harding. Dr Harding graduated from Kings College, University of London, in 1979, with a Bachelor of Science in Microbiology. He gained a PhD in Fungal Pathogenesis from the University of Bath in 1985 and thereafter was in clinical research and medical marketing with Bayer, Merrell Dow, and Marion Merrell Dow for over ten years. He formed a consultancy company in 1992, specialising in clinical research and medical marketing and then founded Micron Research (a UK Clinical Research Organisation) in 1996, which became The Micron Group in 2000 (of which he is President). The Micron Group runs large multi-country clinical studies in all phases of development, and approximately 90% of its business is in the field of anti-infectives.

16. Hospira makes a number of criticisms of Dr Harding's evidence. First, it alleges that he was inconsistent in certain respects, and in particular in relation to common general knowledge at the priority date concerning the efficacy of daptomycin. When considering the insufficiency objection, Dr Harding expressed the view that it was common general knowledge that daptomycin was efficacious at doses of 3-10 mg/kg once every 24 hours. In this context, he stated at [214] of his first report that:

> "The skilled person would have been aware of daptomycin's potent antibiotic activity as a matter of his common general knowledge and would not have doubted that daptomycin would be effective to treat infections in the range of doses covered by the Patent's claims."

17. During his cross-examination, he explained that the skilled team would be aware of daptomycin's efficacy from common general knowledge about Lilly's clinical trials; T6/765/17-24. However, when considering common general knowledge of Lilly's clinical trials in the context of obviousness, he expressed the view that the skilled team would not have known from reports of Lilly's clinical trials (or at all) that daptomycin was efficacious. He expressed this view, for example, at T6/759/3-14.

18. Secondly, Hospira alleges that there were a number of significant places in Dr Harding's written evidence when his quotations from documents were selective, and did not provide a fair reflection of the passages that he cited. In particular, at [50]-[53] of his second report, Dr Harding included a section under the heading "Once-daily dosing of aminoglycosides was primarily for efficacy and convenience, not to reduce toxicity". In support of that proposition, he referred at [52] to the September 1998 BNF, which he did not exhibit. He stated that:

> "This view, that the primary benefits of once-daily aminoglycosides dosing are potentially increased efficacy and improved "ease-of-use", is supported by the fact that clinical dosing recommendations, as set

> out in the BNF in September 1998, did not recommend once-daily dosing. If the once-daily dosing had been primarily driven by, or demonstrated to result in, reduced toxicity, the clinical dosing recommendations would have been revised."

19. The entry from the September 1998 BNF was included in Dr Harding's cross-examination bundle. It stated as follows in respect of once-daily dosage of aminoglycosides:

> "Although aminoglycosides are generally given in 2 to 3 divided doses during the 24 hours, *once-daily administration* has been shown to reduce the risk of toxicity (while ensuring adequate plasma concentrations) but **expert advice** about dosage and plasma concentrations should be obtained" (emphasis in original).

The statement in the September 1998 BNF, that once-daily administration of aminoglycosides had been shown to reduce the risk of toxicity, was contrary to Dr Harding's opinion, and contrary to his account of that document. During his cross-examination, he explained that he thought that the statement in the BNF was wrong, but that he did not feel the need to exhibit it; T6/834/17-835/16.

20. In the same section of his second report, at [51] Dr Harding quoted a sentence from a chapter by Katsung, which Dr Ebert exhibited at SCE-3. He said that:

> "*Numerous clinical studies demonstrate that a single daily dose of aminoglycosides is just as effective and no more (and often less) toxic than multiple smaller doses*" (SCE-3 page 757, start of the third paragraph, emphasis added). As this quotation from SCE-3 makes clear, the main reference to toxicity is that it did not increase when a once-daily dosing regime is used."

However, the next sentence in SCE-3, which he did not cite, supports Hospira's case:

> "Therefore, many authorities now recommend that aminoglycosides be administered as a single daily dose in most clinical situations."

21. It is important to keep criticisms of this nature in perspective. Many witnesses can be accused of inconsistency after a sustained period of cross-examination. Experts have to choose which sections to quote from texts, and it is often suggested that they have not included material passages. I do not consider that Dr Harding was trying to mislead the court in the passages from his evidence to which I have referred. The points made by Mr Meade, however, do have force in relation to the substantive issues to which the relevant evidence was directed, and I shall bear them in mind when considering those issues.

Dr Zeckel

22. Dr Zeckel is a witness of fact who was called by Cubist to give evidence about clinical trials conducted by Lilly in the late 1980s and early 1990s in relation to daptomycin and the reasons why Lilly stopped its development. Hospira makes no criticism of Dr Zeckel as a witness. However, it is alleged that, through no fault of his

own, he was unable to give the full picture about what happened within Lilly in relation to the decision to cease development of daptomycin. In addition, Hospira alleges that Cubist applied, inadvertently, a wrong approach to its disclosure obligations concerning the Lilly history, on which it had chosen to rely, and that it did not disclose material documents adverse to its case. I will consider these issues after dealing with the evidence concerning Lilly's development history.

The Skilled Addressee

23. There was no dispute as to the legal principles that I should apply. In particular:

    i) A patent specification is addressed to those likely to have a real and practical interest in the subject matter of the invention (which includes making it as well as putting it into practice).

    ii) The skilled addressee has practical knowledge and experience of the field in which the invention is intended to be applied. He/she (hereafter "he") reads the specification with the common general knowledge of persons skilled in the relevant art, and reads it knowing that its purpose is to disclose and claim an invention.

    iii) A patent may be addressed to a team of people with different skills. Each such addressee is unimaginative and has no inventive capacity.

    iv) Although the skilled person/team is a hypothetical construct, its composition and mind-set is founded in reality. As Jacob LJ said in *Schlumberger v Electromagnetic Geoservices* [2010] EWCA Civ 819; [2010] RPC 33 at §42:

    > "… The combined skills (and mindsets) of real research teams in the art is what matters when one is constructing the notional research team to whom the invention must be obvious if the patent is to be found invalid on this ground."

24. In the case of the 417 Patent the skilled team would be interested in the development of new or improved treatments for gram-positive infections, and in developing suitable dosage regimens for such treatments. Given the subject matter of the 417 Patent and the problem that it seeks to address, appropriate dosing regimens for antibiotic treatments would be of primary relevance to the skilled team. The team would include individuals with expertise on the clinical aspects of infectious disease, pharmacokinetics and toxicology. The skilled team would also have some knowledge of the clinical trial regulatory process and access to an expert on the regulatory process if required.

Lilly's development history of daptomycin

25. Common general knowledge at the priority date concerning the reasons for Lilly's abandonment of daptomycin in 1991 was a key area of dispute in relation to the 417 Patent. Cubist's answer to obviousness of the 417 Patent rests very heavily on knowledge at the priority date of what it characterised as Lilly's failed development. Mr Waugh QC, who presented Cubist's case on the 417 Patent, submitted that it was generally known at the priority date that daptomycin was a drug which had progressed

through Phase I and some Phase II trials by the early 1990s, but that it had seen clinical failures at lower doses and toxicity at higher doses. A routine literature search on "daptomycin" would reveal further information about the reasons for Lilly's failure. According to Cubist, this would put off the skilled team from trying to develop daptomycin further. By 1998 it would know that Lilly, who were world-leading experts in antibiotics, had failed to bring this drug to market some six years earlier. How, then, could it be obvious to the unimaginative skilled team to develop a successful dosage regimen for this same drug with a fair prospect of success?

26. Before dealing with common general knowledge about Lilly's work at the priority date, it is necessary to find the relevant facts concerning Lilly's daptomycin development, insofar as they can be ascertained from the evidence before the court.

27. According to Dr Zeckel's evidence, Lilly started working on daptomycin during 1985. It was Lilly's goal to develop daptomycin into a safe and effective drug for the treatment of a wide range of gram-positive cocci infections including skin infections, bacteraemia and endocarditis. However, Lilly had a more specific and narrow goal, namely to develop daptomycin as a treatment for endocarditis caused by *Staphylococcus aureus*, which would be superior in respect of efficacy and toxicity to the "gold standard" drug vancomycin, for the treatment of *S. aureus* endocarditis. Dr Zeckel explained this in important evidence at [18] and [20] of his statement:

> "18. Endocarditis can be caused by a number of pathogens. Lilly were targeting a treatment for all forms of endocarditis, but particularly *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* ("**MRSA**") endocarditis. Then, as now, *Staphylococcus aureus* endocarditis is one of the most difficult forms of bacterial endocarditis to treat. Accordingly, Lilly's goal was to develop a drug which could treat these forms of endocarditis, because in doing so, Lilly would then have achieved a treatment for all forms of Staphylococcus infections, including endocarditis…
>
> 20. For these reasons, there was an important clinical need for an antibiotic that would effectively treat both bacteraemia and endocarditis, and which was effective against *Staphylococcus aureus* endocarditis. It was Lilly's goal to develop a drug to address this need with a drug that was at least as safe and effective as vancomycin, but without the associated problems described above."

28. Lilly carried out certain Phase 1 studies in the late 1980s. These studies included (amongst others) a Phase I multiple dose study at 2 mg/kg dosed every 24 hours for 14 days. The first Phase II clinical trial that Lilly carried out (which studied efficacy and side-effects) used a dose of 2 mg/kg once every 24 hours. The results of this study showed a clinical cure or improvement in 96.8% of those with skin and soft tissue infections, which was higher than the reaction to the conventional therapy. Also, the dose of 2 mg/kg once every 24 hours had not demonstrated any appreciable side effects attributable to the drug. However, it did not show the efficacy that Lilly wanted to see in patients with bacteraemia and endocarditis. Dr Zeckel explained this at T2/188/25-189, and went on to explain that the results were encouraging:

> "Q. Now, that trial had some success against skin infections, did it not?
>
> A. It appeared to have some efficacy, yes.
>
> Q. As you say in paragraph 28: "Lilly suspended enrolment in this Phase II study", i.e. the 2 per 24, "in June 1988 because although the results showed efficacy against skin infections, they did not demonstrate the efficacy Lilly wanted to see in patients with serious infections such as bacteraemia and endocarditis."
>
> A. Yes.
>
> Q. Now, actually it was actually quite good against skin infections, was it not, in that trial?
>
> A. Yes, it was a small sample, 31 patients, but it looked like I it could lead to further study."

29. For the purposes of its second Phase II clinical trial, Lilly focused on the treatment of bacteraemia and endocarditis and changed the dosage regimen to a dose of 3 mg/kg every 12 hours. Dr Zeckel was not at Lilly when the decision was made to choose this dosing level and dosing interval. However, he indicated his understanding that there was a view within Lilly that endocarditis required concentrations to be above the minimum inhibitory concentration throughout the treatment period.

30. The second Phase II study demonstrated that the dosing range and interval had efficacy in treating *Staphylococcus aureus* bacteraemia. The doses of 3 mg/kg every 12 hours showed no significant side-effects or any skeletal muscle toxicity ("SMT") symptoms. CPK levels were monitored and very modest elevations were seen in 2 out of 89 patients (Zeckel T2/198/10-199/2). Dr Zeckel considered that the results were "encouraging" and "promising". However, the second Phase II study did not achieve the level of efficacy that Lilly wanted in treating *S. aureus* endocarditis, which, as discussed above, was its specific goal.

31. Lilly's third clinical trial was for a Phase I study of 4 mg/kg every 12 hours. This study resulted in 2 out of 5 people having highly elevated CPK levels, pain in their forearms and grip weakness, which were the clinical symptoms of skeletal muscle toxicity. Dr Zeckel explained at [36]-[38] of his witness statement that normal CPK levels are under 250 units. In the third clinical trial, one volunteer's CPK levels rose above 20,000 units after 11 days and another's rose over 10,000 units after six days. According to Dr Zeckel, Lilly was concerned that continuing the trial would put healthy people at risk in that it was known that patients had developed kidney failure with CPK levels of less than 10,000. Moreover, he suggested that Lilly was concerned that any muscle injury caused by daptomycin administered at this dosage regimen would be more serious in vulnerable patients with potentially life-threatening infections. Dr Zeckel explained that Lilly then suspended the trials and informed the FDA of this fact.

32. Dr Zeckel was cross-examined about an internal meeting held by Lilly on April 10th 1991 to review its daptomycin development. The minutes are contained in an internal

document entitled *Project Management, Medical, Marketing Committee Minutes* ("the 1991 Minutes"). The 1991 Minutes refer to a number of considerations within Lilly which were not mentioned by Dr Zeckel in his witness statement.

33. The first paragraph of the 1991 Minutes records that:

> "Dr C. Rivera and Dr M. Zeckel reviewed the daptomycin project and its clinical status and issues. Mr. G. Stach and Mr. J. Wanko reviewed market economics and a financial analysis. In summary, there was uncertainty regarding the true potential for marked CPK elevations due to the small sample size. The project team recommended termination of the project should the potential for CPK levels be significant since the therapeutic index would be too narrow and the economics unattractive (based on vancomycin (sic) continued dominance in the marketplace without significant resistance)."

This shows that Lilly was of the view that the sample size in the third clinical trial was too small to determine whether the potential for raised CPK levels was significant. Termination of the project was only recommended if the potential for raised CPK levels proved to be significant after further trials. There was a clear concern about the economics of the daptomycin development from Lilly's perspective, given the continuing market dominance of Lilly's vancomycin drug.

34. The 1991 Minutes record that Dr Zeckel proposed that an additional Phase I clinical study should be carried out in relation to a non-endocarditis infection in up to 20 IV drug users starting with a dose of 3 mg/kg every 12 hours, with a target peak of 40-60 mcg/ml. In addition, Dr Zeckel proposed an open label efficacy study in *S. aureus* endocarditis assuming that the initial safety study was completed without incident.

35. The 1991 Minutes conclude that:

> "The committee's recommendation to proceed with the development of daptomycin was contingent on: (a) use of minimal resources to conduct the proposed clinical studies and (b) stipulation that the project's future be revisited in 18 months (or following completion of the two studies) in order to assess the prevalence of vancomycin resistance in the market. The committee further suggested that the team proceed with negotiations with the FDA to conduct these studies. Studies outside of the U.S. would be considered in the event the FDA rejects the proposal."

This shows that Lilly did not decide to discontinue development of daptomycin because of raised CPK levels in 2 patients in the 4 mg/kg Phase II study. It wished to perform further tests and then to revisit the project in order to assess "the prevalence of vancomycin resistance in the market".

36. Subsequent to the April 1991 meeting Lilly decided to cease development of daptomycin. Dr Zeckel had no personal knowledge of why that decision was made. However, a draft of an article by the Vice-President of Infectious Diseases Research at Lilly, Dr Eisenstein, entitled "*Daptomycin: From the Mountain to the Clinic with Essential Help from Francis Tally*" states that the project was discontinued:

> "because the therapeutic window between efficacy and safety was therefore thought to be small taken together with the commercial assessment at Lilly at the time that vancomycin was still reasonably able to deal with infections due to MRSA."

37. Some years later, Cubist became interested in the further development of daptomycin. The notes of a meeting between Lilly and Cubist held on 8 April 1997 record that the parties discussed daptomycin development. Dr Zeckel referred to "Daptomycin's proven efficacy in eradicating staphylococci and enterococcus from bloodstream [bacteraemia] and soft tissues". Cubist then entered into a licence agreement with Lilly, took over the development of daptomycin and performed its own clinical trials.

38. During its development of daptomycin, Cubist was well aware of the positive results of Lilly's clinical trials in the late 1980s/early 1990s. In particular, in a Cubist document sent under cover of a fax dated January 28 1998, Frederick Olsen of Cubist stated as follows, under the heading "*Background: 1986-1991- Eli Lilly Clinical Development of Daptomycin":*

> "Phase II trial #1 showed safety and efficacy in treating skin and soft tissue at 2 mg/kg/day.
>
> Phase II trial #2 showed safety and efficacy in bacteraemia, but unacceptable efficacy in endocarditis at 6 mg/kg/day (3 mg/kg/q.12h).
>
> Reversible adverse muscle effects…evident in two subjects at 8 mg/kg/day (4 mg/kg/q.12h) precluding dose escalation for treatment of endocarditis.
>
> Lilly terminated development in April 1991 since daptomycin would not achieve targeted economic criteria without endocarditis, and at this time, resistant pathogens were not an epidemic."

39. An extract from Cubist's pre-IND, submitted to the FDA in about December 1997 and included in Dr Ebert's cross-examination bundle states at Section E, in relation to the Lilly 2 mg/kg/q. 24h and 3 mg/kg/q. 12h trials, that "there is no evidence from these trials to suggest that doses up to 6 mg/kg/day are associated with muscular or neuronal damage or any other toxicity". It states that the 2 mg/kg/q. 24 hours exhibited good efficacy and may provide better efficacy over resistant infection strains. It states that there was "minimal reversible" SMT at 8 mg/kg/day (4 mg/kg q.12h) and that "all signs of muscle toxicity subsided within several days of discontinuation of treatment".

Conclusion in relation to the Lilly daptomycin trials

40. On the basis of the evidence set out above, I reject Cubist's case, as expressed in [4] of its opening skeleton that "having failed to develop a safe and effective drug Lilly gave up on the drug…". The facts are as follows:

    i) Lilly had set itself the goal of treating a narrow sub-set of gram-positive infections with daptomycin, namely *S. aureus* endocarditis (which was a particularly difficult target).

ii) For other gram-positive infections, including skin and soft tissue infections and bacteraemia, daptomycin had shown success during Lilly's clinical trials in terms of efficacy and had been well-tolerated up to 6 mg/kg per day.

iii) Even in relation to *S. aureus* endocarditis, there was only limited data that a dosage regimen of 4 mg/kg q. 12h (i.e. 8 mg/kg in total per day) had led to raised CPK elevations in 2 out of 5 patients and Lilly proposed further clinical trials to see if this represented a significant risk.

iv) Lilly was concerned that it would not be economically worthwhile to develop daptomycin unless its goal of treating *S. aureus* endocarditis could be achieved, given the market dominance of its vancomycin drug, and this at least contributed to its decision to terminate clinical trials on daptomycin.

Dr Zeckel's knowledge and Cubist's disclosure

41. I can now deal with Hospira's submissions that I should give little or no weight to Dr Zeckel's evidence concerning Lilly's daptomycin development, because he had insufficient personal knowledge to tell the full story and because Cubist has allegedly failed to give proper disclosure of documents in its possession concerning Lilly's history of daptomycin development.

42. Dr Zeckel was not working at Lilly at the time that Lilly decided to go from 2 mg/kg every 24 hours to 3 mg/kg every 12 hours and had no personal knowledge about why this decision was made. Furthermore, he was unable to give evidence about the reasons for the ultimate decision to end work on daptomycin and about the extent to which commercial factors were involved. Hospira submits that there were other witnesses, available from within Lilly and Cubist, who could have given evidence about these issues, but whom Cubist chose not to call.

43. It is true that Dr Zeckel was unable to give evidence from his own knowledge about those issues. My conclusions are based, in part, on the documents which were put to Dr Zeckel in cross-examination, in order to fill gaps in the story.

44. As to disclosure, I do not accept that Cubist was in default of its disclosure obligations in respect of the Lilly history. Cubist's solicitors faced a massive task of selecting documents from US discovery, from which an initial set of 288,000 documents was produced. They were entirely open with Hospira's solicitors as to the approach that they were taking. Hospira was not satisfied with this approach but did not apply to the court to challenge it or to seek specific disclosure. It is true that relevant documents first appeared in the cross-examination bundles prepared by both Hospira and Cubist, and it would have been preferable if both parties had included those documents in their disclosure lists in advance of the trial. It is not appropriate to blame one party for the way in which those documents entered the case. Nor do I consider that either party was prejudiced by the late production of those documents. I consider that I have been able to reach findings of fact in respect of the Lilly history and I have no reason to believe that further disclosure would have changed that position.

Common general knowledge

45. I shall apply the summary of legal principles in respect of common general knowledge set out by Arnold J in *KCI Licensing v Smith & Nephew* [2010] EWHC 1487 (Pat); [2010] FSR 31 at [105]-[115], which was approved by the Court of Appeal at [2010] EWCA Civ 1260; [2011] FSR 8 at [6].

Vancomycin and the need for new treatments for gram-positive infections

46. For many years before the priority date, vancomycin, developed by Lilly, was the "gold standard" treatment for MRSA infections. It was the last line of defence to infections which were resistant to other antibiotics.

47. Cubist points out that by the priority date, there were some generic equivalents to vancomycin. However, there was no evidence that they had penetrated the market to a significant extent in the early 1990s (even if the generics were available at that date) during Lilly's clinical trials of daptomycin. A document disclosed by Cubist in the United States litigation entitled *Product Launch of the Year Q & A - Cubist Pharmaceuticals, Inc.* records that, when Lilly abandoned its daptomycin clinical trials, its vancomycin drug, sold under the brand name Vancocin, "was the leading, branded gram-positive agent generating $400 - 500 million globally." By the priority date in 1998, Dr Ebert explained that there were some generic equivalents available, but they were not used to a great extent because of purity and nephrotoxicity issues.

48. Hospira contends that at the priority date (and in 1992) there was a need for new/alternative treatments for all gram-positive infections. However, the level of need and the reasons for the need varied over time and between different types of infection.

49. Cubist points out that this need arose well before the priority date. In particular, it relies on a passage from the 1997 edition of Strohl W.R. Biotechnology of Antibiotics Chapter 1 *Industrial Antibiotics: Today and Future*:

> "Thus, for several years there was an attitude that if nothing else worked, at least vancomycin would. This illusion was shattered when the discovery of vancomycin resistant enterococci in England and France was reported in 1987."

50. I accept that there was a need for an alternative to vancomycin for some years before the priority date. However, Dr Harding agreed that by 1998 there was an alarming increase in the amount of strains of pathogens that were resistant to antibiotics. This concern applied to all infections discussed in this case, including skin and soft tissue, bacteraemia and endocarditis. Dr Harding said that, as compared to 1991/1992, by 1997/1998 there was a reason to re-assess potential treatments and new agents for treating resistant strains of gram-positive infections (including skin infections), T6/794/13-795/7. In my judgment, this was common general knowledge:

> "A. It was a common theme. Everybody was looking at new agents for Gram-positive infection.
>
> Q. Yes, they were looking with urgency for something that could tackle MRSA infections, because of the rise of resistance?

A. Correct.

Q. So there would be a greater incentive to take daptomycin forward potentially than there would have been around about 1991/92?

A. Yes."

51. It was also common general knowledge that there was a specific issue in relation to the treatment of endocarditis, and within that class *S. aureus* endocarditis was particularly difficult to treat. It was well known that *S. aureus* endocarditis was "the toughest nut to crack" for a new treatment. By contrast, it was well known that skin and soft tissue infections were easier to treat than endocarditis; Harding XX T6/789/4-14.

Common general knowledge/what would have been found out about the Lilly trials

52. Dr Ebert stated at [4.46] of his first report, and I accept, that it was common general knowledge at the priority date that daptomycin was a potent lipopeptide antibiotic discovered by Lilly in the 1980s, which was known to be bactericidal against a broad range of gram-positive pathogens. He also stated, and Dr Harding agreed, that by September 1998, a number of daptomycin clinical studies had been carried out by Lilly in humans. The skilled person would have been generally aware of this, and of the fact that Lilly had not pursued daptomycin further. It was also common ground that the skilled team interested in daptomycin at the priority date would conduct a literature search on daptomycin to discover what had been published about it and its relevant properties.

53. I do not consider that in 1998, this literature search would have been confined only to an electronic search as Dr Ebert explained, and I accept, that the skilled person in 1998 would normally have attended two or three of the regular scientific meetings and conferences that took place every year. Of particular importance was the meeting of the Interscience Conference of Antimicrobial Agents and Chemotherapy ("ICAAC"). In 1998 ICAAC was attended by more than 15,000 participants from all over the world. The experts were clear about the importance of "ICAAC" meetings at the priority date, and in my judgment, key abstracts from such meetings concerning daptomycin would have been located and considered by the skilled team.

54. Dr Harding performed a literature search which commenced at the beginning of 1992. This was nearly a year after Lilly had put its clinical trials of daptomycin on hold, and excluded various publications by Lilly about those clinical trials. In particular, it excluded information about the favourable outcomes of those trials. In my view, the skilled team performing a literature search at the priority date on daptomycin would have included literature published before the beginning of 1992, in order to gain some understanding of the reasons why Lilly discontinued the clinical trials.

55. More generally, Cubist's case depended on the proposition that the skilled team would gain an inaccurate understanding of the results of Lilly's clinical trials from the literature search at the priority date. They would not know or learn that doses of 2 mg/kg once a day had succeeded in certain infections, including skin and soft tissue; nor that 3 mg/kg twice a day (i.e. a total daily dose of 6 mg/kg) had succeeded in bacteraemia and endocarditis other than *S. aureus* endocarditis with only mild CPK

elevations and no clinical symptoms. Dr Harding's view was that the skilled team would be aware that the Lilly trial at 3 mg/kg per 12 hours had resulted in "therapy limiting toxicity" and more generally of "efficacy and toxicity issues" with daptomycin (Harding (1) [168] and [193]). Cubist's case, as put to Dr Ebert, was that the skilled team would know or learn from the published literature that daptomycin had not been sufficiently efficacious at lower doses, and that higher doses had caused toxicity issues. I do not accept that this vague and inaccurate perception is a fair reflection of what the skilled team would have learnt from the published literature. I will set out a brief summary of the most relevant literature before reaching my conclusions on this issue.

56. Abstracts of the 1988 ICAAC include an abstract by Sexton et al. *The use of daptomycin, a lipopeptide antibiotic, in the treatment of gram-positive infections in man* ("Sexton et al"). Sexton et al reports the results of clinical trials at Lilly at 2 mg/kg once-daily. It states that:

> "Daptomycin (D), a semisynthetic lipopeptide antibiotic highly effective in vitro against gram-positive organisms, was administered i.v. once-daily in a dose of 2 mg/kg to patients with various types of susceptible gram-positive infections and compared to conventional (vancomycin etc.) therapy (C) using a double-blind, randomised study design… The results from this study showed that i.v. daptomycin in a dose of 2 mg/kg /day may be safe and effective in patients with various gram-positive infections."

57. A paper was published by Garrison et al entitled *Suboptimal effect of daptomycin in the treatment of bacteraemias* in the Southern Medical Journal (1989). This describes two patients with complex and serious infections to whom doses of 2 mg/kg per 24 hours of daptomycin were administered and in whom the therapy was reported to be unsuccessful. The authors conclude that the findings in these two patients suggest that a larger dose of daptomycin or a shorter dosing interval or both might be required to treat seriously ill patients adequately. Whilst this paper was only concerned with two patients with severe underlying conditions, one option that it contemplated was a dose of daptomycin higher than 2 mg/kg per 24 hours.

58. Abstracts of the 1991 ICAAC include an abstract by Lee et al. *Daptomycin versus conventional therapy in the treatment of endocarditis and bacteraemia* ("Lee et al"). Lee et al reports the results of Lilly's clinical trials of daptomycin (D) at 3 mg/kg once every 12 hours, compared with conventional therapy (C). This is reported as a multicentre, prospective, randomised, open-label trial in endocarditis (E) and bacteraemia (B) due to gram-positive pathogens. The results suggest less efficacy for the treatment of *S. aureus* endocarditis (SAE) than for the other infections, where the message was positive. Only two patients were recorded as having CPK elevations which was not expressed to be a matter of concern. The overall conclusion from these clinical trials was positive for bacteraemia and endocarditis other than *S. aureus* endocarditis:

> "These results suggest that D at 3 mg/kg/12h, while effective in B and non-SAE, may be less effective in SAE. Higher doses of D may be necessary to achieve improved success rates in SAE."

59. A paper was published by Rybak et al. *Pharmacokinetics and bactericidal rates of daptomycin and vancomycin in intravenous drug abusers being treated for gram-positive endocarditis and bacteraemia* Antimicrob Agents Chemother. 1992 May; 36(5): 1109-1114 ("Rybak et al"). This paper states that early clinical trials utilising 2 mg/kg per day of daptomycin were "suspended because of unexplained treatment failures in patients with bacteraemia and endocarditis". It indicates that the reasons for this failure are unclear but that it may be because of daptomycin's protein binding. This indicates that higher doses of daptomycin per day might be efficacious. The paper then reports a trial of daptomycin at 3 mg/kg every twelve hours, which was suspended in December 1990 "because of treatment failures in patients with *S. aureus* endocarditis." Rybak et al reinforces the message of Lee et al that there might be a difficulty in successfully treating *S. aureus* endocarditis with daptomycin, but does not contain evidence to support the same difficulty with other infections.

60. A paper was published by Caron et al. *Daptomycin… for treatment of experimental endocarditis due to a highly glycopeptide-resistant isolate of enterococcus faecium* Antimicrob Agents Chemother. 1992 December; 36(12): 2611-2616 ("Caron et al"). Caron et al states that:

> "failures of daptomycin to cure Staphylococcal human endocarditis have been reported recently (8,14), suggesting that higher doses should be used to obtain adequate unbound concentrations of daptomycin in serum."

Caron et al also states that:

> "Daptomycin has recently been withdrawn from further clinical testing because of its failure against human endocarditis as well as its toxicity."

61. This latter statement, whilst generalised and inaccurate, lends some support to Cubist's case. However, I do not consider that it would be read in isolation from the rest of the literature. In addition, when read with the first passage cited above, it would indicate to the skilled team that the failures referred to were in Staphylococcal endocarditis.

62. A paper was published by Lamp et al. *In vitro pharmacodynamic effects of concentration, pH, and growth Phase on serum bactericidal activities of daptomycin and vancomycin* Antimicrob Agents Chemother. 1992 December; 36(12): 2709-2714 ("Lamp et al"). Rybak was also an author, and Lamp et al repeats some statements from Rybak et al. In particular, Lamp et al contains the following passages:

> "Daptomycin was studied in early clinical trials with a dosage of 2 mg/kg of body weight per day. These trials were terminated because of failures despite seemingly adequate levels in serum. The most recent clinical trials with daptomycin were suspended because of failures in patients treated for *Staphylococcus aureus* endocarditis." …
>
> "Endocarditis represents a unique infectious process which includes difficulties existing in both antibiotic penetration, impaired immune

> response, high bacterial inoculum, and bacteria in both logarithmic and stationary growth Phases."…
>
> "Despite seemingly excellent in vitro activity and in vivo efficacy in animal models, daptomycin has proved ineffective against human *S. aureus* endocarditis in the dosage regimens administered to date. Daptomycin has been dropped from further development in the United States because of the toxicity with higher dosage regimens. This study has demonstrated that despite the harsh environmental conditions evaluated, daptomycin was capable of producing kill rates surpassing those of vancomycin."

63. As with the other literature, Lamp et al indicates problems experienced with attempting to treat *S. aureus* endocarditis with daptomycin.

64. The textbook *Biotechnology of Antibiotics (Drugs and the Pharmaceutical Sciences)* 2nd edition, 1997 contains a chapter by Baltz entitled *Lipopeptide Antibiotics Produced by Streptomyces roseosporus and Streptomyces fradiae* ("Baltz"). Hospira submits that there is no reason why a skilled person, interested in dosage regimens for daptomycin, would find and read Baltz. I do not accept this submission. Baltz was from Lilly Research Laboratories, his work would be read with interest, and it was cited in a paper by McHenney et al *Molecular Cloning and Physical Mapping of the Daptomycin Gene Cluster from Streptomyces roseosporus* Bacteriol. 1998 January; 180(1): 143-151, which the skilled team would have found on a literature search.

65. Under the heading "Clinical Studies", Baltz says, amongst other things:

> "Daptomycin was shown to be well tolerated in normal human volunteers when given intravenously in a 30 or 60 minute infusion at 1 or 2 mg/kg every 24 hrs (41,57). Woodworth et al. (58) also studied the safety, pharmacokinetics and disposition of daptomycin in healthy volunteers. They showed that in single intravenous doses infused over 30 min, daptomycin was well tolerated at 0.5 to 6.0 mg/kg per day…. The authors caution that the high protein binding and large molecular size of daptomycin may limit the distribution of daptomycin out of the plasma, and so daptomycin treatment of deep-seated infections, such as bone infections and endocarditis, may have limited effectiveness."

66. This passage is encouraging about the tolerance for daptomycin in humans at the doses stated, which includes 6 mg/kg per day. Its reservations as to efficacy concern "deep-seated" infections, such as bone infections and endocarditis.

67. Baltz continues:

> "At a dose of 2 mg/kg every 24 hr, daptomycin was shown to be effective in treating a variety of Gram-positive infections (59). In another study, daptomycin given at a dose of 3 mg/kg every 12 hr was shown to be effective in treating Gram-positive bacteraemias and endocarditis caused by Gram-positive pathogens (including E. faecalis) other than *S. aureus* (60). Only two of seven patients with *S. aureus* endocarditis had successful outcomes. Five patients were discontinued

> from the study because of adverse effects. In another study, daptomycin at 2 mg/kg once a day failed to treat two very seriously ill patients with Gram-positive infections (61). It was suggested in the latter two studies that higher doses of daptomycin would be required to treat *S. aureus* endocarditis and severely ill patients. However, the occasional adverse effects noted at a dose of 3 mg/kg every 12 hours seem to preclude raising the dose further, and clinical trials were stopped."

68. Hospira points out that the suggestion in Baltz that, as a result of occasional adverse effects noted at a dose of 3 mg/kg every 24 hours, clinical trials were stopped by Lilly, is not accurate. More importantly, Baltz is encouraging as to the results of trials for infections other than *S. aureus* endocarditis, and its main concern is about raising the dose beyond 3 mg/kg every 12 hours i.e. to a dose higher than 6 mg/kg every 24 hours.

69. In respect of the clinical trials, Baltz concludes by saying that:

> "Daptomycin was successful in clinical trials at treating some Gram-positive infections, but it failed to treat staphylococcal endocarditis adequately. Elevated doses of daptomycin suggested that it may cause muscle toxicity in some patients, and so the clinical trials were stopped."

70. It was clear that the skilled team would not find out about Lilly's clinical trial at 4 mg/kg every 12 hours, nor the results of that trial. Dr Zeckel explained that this information was not published.

71. Drawing together the information that was published in 1998, in my judgment the skilled team would discover from a literature search that Lilly's clinical trials had been successful in treating some gram-positive infections, including skin infections, bacteraemia and certain strains of endocarditis. It would also discover that Lilly had not been able to treat *S. aureus* endocarditis successfully at the doses of daptomycin that had been administered, and it would know that this was the hardest infection to treat. It might be concerned about raising the total dose beyond 6 mg/kg but the available evidence indicated that daptomycin was safe and efficacious for infections other than *S. aureus* endocarditis up to this total daily dose.

Skeletal muscle toxicity

72. Hospira submits that SMT is usually reversible and that Lilly never encountered the highest level of SMT that would cause serious and lasting clinical problems such as rhabdomyolysis (acute renal failure). That is true. However, Dr Harding's evidence was that SMT is classed as a serious adverse event and the normal response to marked elevations in CPK such as experienced by Lilly in two patients was to halt further administration.

73. In my judgment, marked elevations in CPK levels in two patients could be indicative of a health risk, but more investigation would be required to determine whether this would be the case. Lilly's own view at the time was that the sample size was too small to determine whether the potential for raised CPK levels was significant. Termination

of the project was only recommended if the potential for raised CPK levels proved to be significant after further trials. This view would, I believe, have been shared by the notional skilled team.

Tolerance of side effects

74. It was well known at the priority date that the extent to which side effects would be deemed acceptable for a new treatment for gram-positive infections depended on a number of factors, including the severity of the infection compared with the severity of the side effects, and the absence of alternative treatments for resistant bacterial strains.

Advantages of once-daily dosing

75. The experts were agreed that whilst safety and efficacy would be the primary considerations, there were practical benefits to once-daily dosing which were common general knowledge at the priority date. Dr Harding explained at [60]-[62] of his first report that once-daily dosing is easier for patients and medical professionals to comply with. It means that the time required to prepare and administer the antibiotic is reduced and scheduling is easier.

76. In particular, once-daily dosing is desirable, even where the patient is hospitalised, to maximise convenience, minimise the chances of missed doses and ensure clinical success. Furthermore, drugs that can safely and effectively be dosed once-daily, even those administered intravenously, are suitable for use in outpatient antibiotic therapy, which means that the patient can be discharged from hospital once the signs have resolved or improved sufficiently, rather than remaining in hospital for the entire period of his/her treatment. Dr Ebert agreed with Dr Harding as to the known practical benefits of once-daily dosing. Dr Ebert summarised this at [3.2] of his second report, and I accept his evidence:

> "if a once-daily dosing regimen had a similar efficacy and safety profile to a twice-daily dosing regimen, the skilled person would pursue the once-daily dosing regimen due to the practical benefits."

Pharmacodynamic and pharmacokinetic principles

77. Dr Ebert explained, and I accept, that there were certain widely known pharmacokinetic and pharmacodynamics principles which in 1998 would have been used in developing an optimal antibiotic dosing regimen. The object was to maximise its therapeutic effect, while minimising its negative or toxic effect. These principles included:

i) minimum inhibitory concentration ("MIC"), which is the smallest concentration of an antibiotic that inhibits growth of target pathogens;

ii) minimum bactericidal concentration ("MBC") which is the smallest concentration of an antibiotic that kills greater than 99.9% of bacteria;

iii) maximum/minimum serum concentration ("Cmax" and "Cmin"). Cmax is the maximum, or peak, serum concentration achieved by the antibiotic after it has been administered. Cmin is the minimum, or trough, serum concentration

achieved prior to administration of the next dose. A larger dose administered less frequently will result in a higher Cmax and a lower Cmin. A smaller dose administered more frequently will result in a lower Cmax and a higher Cmin.

iv) Area under the curve ("AUC") which is a measure of the overall exposure of the body to the drug over a given time period. Because the AUC is a measure of the overall exposure, it is generally not influenced by a change in the dosing interval or the amount dosed, as long as the same total daily dose is administered.

v) Half-life (t½) which refers to the time required for serum concentrations of the drug to decline by 50%. A drug with a longer half-life may usually be administered less frequently than drugs with short half-lives.

vi) Drug protein binding which refers to the fraction of drug in the blood that is reversibly bound to certain serum proteins. It was generally believed that a drug that is protein-bound is biologically inactive and/or cannot enter into sites outside the bloodstream where it may be required to produce a therapeutic effect. A drug that displays a high level of protein binding has a small amount of free-circulating drug available to achieve the desired therapeutic effect.

Concentration dependent killing

78. There was some dispute between the experts concerning common general knowledge in this area. It was well known that there was a distinction between time-dependent killing antibiotics and concentration-dependent killers. In the case of time-dependent killers it was important to maintain the drug concentration above the MIC for as long as possible. By contrast, for concentration-dependent killers, the drug does not need to stay above the MIC for as long as possible; Harding XX T6/608/17-25; T6/849/6-13.

79. Dr Harding suggested in his reply report that within the group of concentration-dependent killers there are two subclasses: those which achieve increased bactericidal activity with increased AUC (a higher ratio of AUC: MIC) and those which achieve bactericidal activity with increased Cmax (a higher ratio of Cmax: MIC). However, his cross-examination made clear at T6/847-849 that for both of these subclasses, the Cmax was important for efficacy and neither subclass required that the drug be kept above the MIC for as long as possible. Indeed, Dr Ebert explained, and I accept, that it was an oversimplification to treat concentration-dependent killers as being clearly severable between these two subclasses, as all antibiotics have the AUC as one of the drivers.

80. For concentration-dependent killers, Dr Ebert explained, and I accept, that the goal of therapy was to maximise bacterial killing by achieving as high a concentration of the drug in the blood as possible during the dosing interval. For a given daily dose, this was best accomplished by extending the dosing interval and administering higher doses at each interval. There was no need in the dosing regimen to keep the drug above the MIC. There was also a tendency to aim for a higher Cmax through less frequent doses to prevent the emergence of resistance over time.

Aminoglycosides and quinolones

81. The two classes of concentration-dependent killers used to treat infections in humans which were discussed in the evidence were aminoglycosides and quinolones.

82. Dr Harding disputed that it was common general knowledge that aminoglycosides and quinolones were capable of being administered, and were administered, at a higher dose less frequently. He pointed out that the primary goal with concentration-dependent killers was to achieve a high Cmax, which could be accomplished by administering a sufficiently high dose of the antibiotic. He explained that it does not follow that the high dose is automatically accompanied by an extension of the dosing interval. There are other considerations beyond Cmax, in particular the need to ensure that the drug is efficacious whilst avoiding administration at levels which might cause toxicity.

83. I accept that the balance between efficacy and toxicity would always be a consideration in the determination of dosage regimens and that it would not automatically follow that a high dose would be accompanied by an extension of the dosing interval for concentration-dependent killers. However, I find that it was common general knowledge at the priority date that aminoglycosides could be dosed, and were being dosed, once-daily, and that this provided good efficacy with no increase, or even a potential reduction, of toxicity as compared with a dosing regimen of twice a day.

84. This was established by the BNF 1998, which stated in relation to aminoglycosides that "once-daily administration has been shown to reduce the risk of toxicity (while ensuring adequate plasma concentrations) but expert advice about dosage and plasma concentration should be obtained." Similar information was contained in a textbook by Katzung *Basic & Clinical Pharmacology*, seventh edition (1997), which stated that "numerous clinical studies demonstrate that a single daily dose of aminoglycosides is just as effective and no more (and often less) toxic than multiple smaller doses."

85. During his cross-examination Dr Harding referred to meta-analyses that had been conducted, suggesting that toxicity and efficacy were not improved by moving to once-daily dosing. I do not consider that the meta-analyses suggested any more than that toxicity needed to be monitored for patients receiving a once-daily dose of aminoglycosides. Indeed, an editorial by Gilbert published in *Clinical Infectious Diseases* (1997) was entitled "Meta-Analyses Are No Longer Required for Determining the Efficacy of Single Daily Dosing of Aminoglycosides". The editorial concluded with information that I consider was common general knowledge at the priority date:

> "SDD [single daily dosing] appears to be a safe and efficacious approach that does not prevent drug toxicity but may reduce the risk. SDD of aminoglycosides is simpler, less time-consuming, and intuitively more cost-effective than traditional MDD [multiple daily dosing] regimes."

86. At [4.33] of his first report, Dr Ebert stated that fluoroquinolones were another example of concentration-dependent killing drugs where greater bactericidal killing was achieved by administering a higher dose less frequently rather than by

administering a lower dose more frequently. At [48] of his reply report Dr Harding suggested that within the classes of quinolones and fluoroquinolones, not all drugs were administered once-daily. He gave the examples of oxolinic acid (with a half-life of 6 to 7 hours and 80 to 85% protein binding) which was dosed twice daily; and of pefloxacin and levofloxacin, (with half lives of 10.5 hours and 5 to 8 hours respectively), which were dosed twice daily, for most serious infections.

87. The cross-examination of Dr Harding established that oxolinic acid was a very old drug that was only used in veterinary applications. Pefloxacin and levofloxacin were dosed once or twice daily depending on the indication and severity of the condition.

88. In conclusion, all of the concentration-dependent killers used to treat infections in humans that were referred to in the evidence were well known at the priority date to be capable of being dosed once-daily, and the advantages of once-daily, as compared with multiple daily dosing, were also well-known.

Post-antibiotic effect ("PAE")

89. PAE occurs both in vivo and in vitro, and is a characteristic of most antimicrobial drugs. It refers to the persistent suppression of bacterial growth after exposure to an antibiotic. In general, antibiotics exhibiting a prolonged PAE can be dosed less frequently whilst maintaining adequate bacterial inhibition. In vivo PAEs were not normally measured in humans, so it was necessary to extrapolate from in vitro tests and in vivo animal models to estimate the duration of the in vivo PAE in humans. It was well known that in vitro PAEs were shorter in duration than would actually be found in vivo, as Dr Ebert explained in cross-examination. I accept his evidence. It is supported by Craig, *Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men*: Clinical Infectious Diseases (1998) where the author states that "in most cases, in vivo PAEs are longer than in vitro PAEs."

90. In his reply report at [32] Dr Harding disputed Dr Ebert's evidence that the PAE was a well-known factor at the priority date to take into account when considering dosing regimens. He did not maintain this in his cross-examination (T6/806/18-807/15).

The pharmacokinetic and pharmacodynamic properties of daptomycin

91. Dr Ebert's view was that it would have been common general knowledge at the priority date that daptomycin was (a) a concentration-dependent killer with (b) a long serum half life (eight hours): (c) high serum protein binding (over 90%); and (d) a long PAE (>6 hours at clinically achievable serum concentrations).

92. Dr Harding disagreed with Dr Ebert that the specific properties of daptomycin would have been common general knowledge. This dispute was, however, immaterial, since Cubist accepted that the first three properties of daptomycin would have been found from a literature search, and it is common ground (and part of Cubist's case) that such a literature search would have been performed by the skilled team at the priority date. The only dispute was in relation to the value for PAE. However, that dispute was relatively narrow because Dr Harding accepted during his cross-examination that the skilled person would readily find out that daptomycin had a significant PAE, and that a number of its key pharmacokinetic and pharmacodynamic properties were similar to those of the aminoglycosides (T6/828/19-829/10).

93. During his cross-examination, the Hanberger and Bush papers were put to Dr Ebert, which showed a range of values in vitro for the PAE of daptomycin, certain of which were below 6 hours (in vitro PAE in Hanberger of 0.6-6.7 hours, and in Bush of 2.5-5.3 hours). Hanberger indicated that further studies would be needed to rationalise the results. However, the evidence established that it was common general knowledge that the in vivo PAE would be higher than that shown in vitro. Furthermore, Dr Ebert explained that the PAE of interest to the skilled person would be those at clinically achievable concentrations and that would not include all of the PAEs in the ranges shown in Hanberger and Bush.

94. Dr Ebert considered that it would be reasonable to assume that the in vivo PAE of daptomycin would be more than six hours. I accept his evidence. His opinion is clearly supported by Baltz and I have accepted Cubist's case that the skilled person would have read Baltz with interest on a literature search. Baltz considered the Hanberger paper at page 424 and concluded from its results on daptomycin that "the PAEs at clinically achievable concentrations were still >6 hr."

Paediatric dosing

95. Cubist submits that no paediatric development or use of an antibiotic will be undertaken unless it has been established that the drug is safe and efficacious in adults. Furthermore, children cannot be treated as little adults and separately designed and conducted studies need to be carried out. In addition, it submits that in paediatric patients, a shorter dosage interval is often used.

96. I find that it was common general knowledge that in general, adult doses of antibiotics, when expressed as mg/kg would need to be increased in children to take account of their relatively high rate of drug clearance. Dr Ebert provided an equation to calculate this which Dr Harding accepted in cross-examination would readily have been found in routine literature searches. It was not established by Cubist that if a drug was used with a single dosing interval in adults it was common for a shorter dosing interval to be used in children.

The 417 Patent

97. [0001] of the 417 Patent states that its invention relates to improved use of daptomycin, with potent bactericidal activity against gram-positive bacteria, including antibiotic-resistant strains. [0002] states that:

> "The rapid increase in the incidence of gram-positive infections including those caused by resistant bacteria has sparked renewed interest in the development of novel classes of antibiotics. One such class is the lipopeptide antibiotics, which includes daptomycin."

This is consistent with the common general knowledge that in the years leading up to the priority date there was an alarming increase in the amount of strains of pathogens that were resistant to antibiotics and that by the priority date, there was a reason to re-assess potential treatments and new agents for treating resistant strains of gram-positive infections.

98. [0002] also explains daptomycin has potent bactericidal activity in vitro against clinically relevant gram-positive bacteria that cause serious and life-threatening diseases. It states that these bacteria include resistant pathogens, such as vancomycin-resistant enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), glycopeptide intermediary susceptible Staphylococcus aureus (GISA), coagulase-negative staphylococci (CNS), and penicillin-resistant Streptococcus pneumontas (PRSF), for which there are very few therapeutic alternatives. It states that "Daptomycin provides a rapid, concentration-dependent bactericidal effect arul (sic) a relatively prolonged concentration-dependent post antibiotic effect in vivo." This is consistent with the information that the skilled team would have learnt on a literature search before the priority date, namely that daptomycin is a concentration-dependent killer and that its PAE, which was an important property in relation to dosing, was relatively prolonged in vivo.

99. [0003] is relevant to Hospira's insufficiency attack based upon the description of daptomycin in all of the Patents. I will consider it when dealing with this issue.

100. [0004] suggests that daptomycin's mechanism of action is distinct from that of other classes of antibiotics and theorises as to what the mode of action of daptomycin might be.

101. [0005] purports to summarise the various nonclinical and clinical Phase I and Phase II trials that had been undertaken to examine the efficacy and safety of daptomycin. The 417 Patent indicates that:

i) Daptomycin was well tolerated in human volunteers when given at 1 or 2 mg/kg every 24 hours.

ii) A single dose of daptomycin was well tolerated over a dose range of 0.5 to 6 mg/kg, citing Baltz and Woodworth.

iii) A single dose formula was well tolerated when administered with another antibiotic.

iv) Prolonged treatment of 3 mg/kg every 12 hours caused "occasional adverse effects", citing Baltz.

v) Treatment of 4 mg/kg every 12 hours for 6 to 11 days led to two of five human patients having transient muscular weakness, with elevated CPK levels, citing Tally et al, published in 1999, subsequent to the priority date. The 417 Patent states that the treatment was discontinued three to four days after initial elevation in CPK levels. It states that "One or two days after discontinuation of daptomycin treatment, CPK levels peaked at levels in excess of 10,000 U/L in one subject and at 20,812 U/L in the second subject."

vi) The last sentence of [0005] states that "Based upon these studies and the rationale that higher doses of daptomycin were required for efficacy against many types of bacterial infection, clinical studies of daptomycin were discontinued" (citing Baltz).

102. [0006] refers to skeletal muscle toxicity as the primary toxicity associated with daptomycin and refers to toxicology studies in animals where repeated daily administration of 75 mg/kg/day in rats and 40 mg/kg/day in dogs caused mild myopathy in the skeletal muscle.

103. [0007] states that:

> "Although low doses of daptomycin do not cause muscle toxicity and are effective in treating many gram-positive bacterial infections, certain types of gram-positive bacterial infections, such as deep-seated infections or those caused by certain antibiotic resistant bacterial strains, may require higher doses of daptomycin for effective treatment. For instance, certain vancomycin resistant strains of bacteria exhibit a to-24-fold higher daptomycin minimum in inhibitory concentration MIC than most vancomycin-susceptible strains. Accordingly, there is a great need to develop methods for administration of effective amounts of daptomycin that will also minimise adverse skeletal muscle effects."

104. This acknowledges that low doses of daptomycin do not cause muscle toxicity and are effective in treating many gram-positive bacterial infections; it indicates that deep-seated antibiotic-resistant bacterial infections require higher doses of daptomycin and that it is for that sub-set of gram-positive infections that there is said to be an issue with minimising the adverse effects of skeletal muscle toxicity.

105. [0009] acknowledges that aminoglycosides are also toxic at high doses and have been administered at a high dose at less frequent intervals rather than at lower doses at more frequent intervals in order to reduce their toxicity. However, it asserts that aminoglycosides differ from daptomycin in a number of ways and so the possibility that less frequent administration of aminoglycosides results in lower toxicity does not predict that the same would be true for daptomycin. I will consider this assertion when dealing with obviousness in the light of Woodworth.

106. The Summary of the Invention is then set out at [0010]-[0012]. It is said that the invention addresses the problem of SMT at high doses of the lipopeptide antibiotic daptomycin and provides the use of the antibiotic in a manner that minimises SMT while simultaneously maintaining a sufficient efficacy level. [0012] states that:

> "The invention is characterised by a pharmaceutical composition comprising a high dose of the antibiotic that causes skeletal muscle toxicity at a dosage interval of 24 hours to once weekly. In one embodiment of the invention, daptomycin is administered at a dose of 3 to 75 mg/kg at a dosage interval of 24 hours to once weekly."

This is explained by the fact that in the 417 Patent as granted, claim 1 was not limited to a dosage regimen of 3 to 10 mg/kg every 24 hours. The range was far wider, as was the dosage interval.

107. The description goes on to refer to two dog studies which were carried out. Example 1 (Study A) describes a study in dogs with regimens of daptomycin at 25 mg/kg every 24 hours, 75 mg/kg every 12 hours and 25 mg/kg every eight hours for 20 days, in

order to analyse the relationship between Cmax and AUC, and SMT. Example 2 (Study B) describes a study in dogs with regimens of daptomycin at 5 mg/kg every 24 hours and 5 mg/kg every 8 hours for 20 days, in order to analyse the relationship between threshold plasma and SMT.

108. Based on Studies A and B in Examples 1 and 2, the 417 Patent suggested at [0017]-[0018] that muscle toxicity is not primarily related to Cmax and that toxicity does not appear to be related to AUC or to an intrinsically toxic plasma concentration, but rather to the dosing interval of daptomycin. It states that:

> "Without wishing to be bound by any theory, skeletal muscle effects appear to be related to the duration of time at low plasma concentrations of daptomycin available for repair of subclinical damage to the myofibers. Therefore, the data suggest that the dosing interval is the key determinant of muscle toxicity, rather than just the magnitude of the dose itself. Further, since Cmax and/or AUC were found to be the key pharmacokinetic parameters associated with eradication of infection [refs cited] the pharmacological activity of daptomycin is optimized by once-daily dosing. These results suggest that once-daily dosing can minimize daptomycin muscle toxicity, while potentially optimizing its antimicrobial efficacy (Figure 3)."

109. Example 4 provides the results of a clinical study on adult patients with serious gram-positive bacteraemia or vancomycin resistant infections. The subjects were treated for a period of 7 to 21 days. The data sets out the CPK results following administration of daptomycin to 8 patients at 4 mg/kg every 24 hours, 9 patients at 6 mg/kg every 24 hours, and 3 patients at 6 mg/kg followed by 3 mg/kg every 12 hours. The 417 Patent states at [0050] that:

> "The results demonstrate that administration of daptomycin to eight patients at a 4 mg/kg dose every 24 hours or to nine patients at a 6 mg/kg dose every 24 hours did not cause an increase in serum CPK levels above the normal range… Furthermore, even in the few patients who experienced some elevation in CPK levels above normal, the elevation was not considered to be related to daptomycin treatment… Similarly, administration of an initial dose of 6 mg/kg daptomycin followed by 3 mg/kg every 12 hours to three human patients did not cause an increase in CPK levels above normal."

110. Example 5 is a prophetic example of a human study in patients with gram-positive bacterial infections with different doses every 24 hours, every 28 hours and every 72 hours. The doses will include 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 or 25 mg/kg. The study has not yet been performed and so no data are provided.

The Claims

111. The claims in issue are those which are the subject of the unconditional amendment application. In proposed amended form, they are as follows:

> 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.
>
> 2. The use according to claim 1 wherein the dose is 3 to 10 mg/kg but excluding 3 mg/kg.
>
> 3. The use according to claim 1, wherein the dose is 3, 4, 5, 6, 7, 8 or 9mg/kg.
>
> 4. The use according to claim 3 wherein the dose is 4 mg/kg.
>
> 5. The use according to claim 3 wherein the dose is 6 mg/kg.
>
> 6. The use according to claim 3 wherein the dose is 8 mg/kg.
>
> 7. The use according to claim 3 wherein the dose is 10 mg/kg.

Scope of the claims

112. The claims include the functional technical feature of being able to treat bacterial infections at the dose range and in the dose interval specified (3 to 10 mg/kg once every 24 hours). None of the claims are limited to any type of bacterial infection and they include use of daptomycin for the treatment of skin and soft tissue infections, bacteraemia and all strains of endocarditis. Specifically, none of the claims are limited to the treatment of *S. aureus* endocarditis.

113. A practical construction of the claims means that daptomycin at the dose range and dose interval claimed cannot have such severe side-effects as to preclude its use in the treatment of a human patient. However, the claims do not require any particular reduction in toxicity, nor that CPK levels in patients will remain below a specified amount, nor that SMT must be reduced or eliminated. This is evident from the absence of such limitations in any of the claims.

Priority

Legal principles and the effect of G 2/98

114. General principles to be applied in respect of entitlement to priority were summarised by Kitchin LJ in *Medimmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234; [2103] RPC 27. In particular:

    i) A claim to priority of the "same invention" is referred to in Article 87(1) of the European Patent Convention. Section 5(2)(a) of the Patents Act 1977, which provides for entitlement to priority, is to be interpreted as having the same effect as Article 87(1), pursuant to section 130(7) of the Act; *Medimmune* at [151].

    ii) The requirement for the "same invention" means that priority 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 priority document as a whole; G 2/98 *Same Invention* [2001] OJ EPO 413; [2002] EPOR 167.

iii) The approach is not formulaic: priority concerns technical disclosure, explicit or implicit. The question is whether there is enough in the priority document to give the skilled person essentially the same information as forms the subject of the claim and enables him to work the invention in accordance with that claim; *Unilin Beheer v Berry Floor* [2004] EWCA (Civ) 1021; [2005] FSR 6 at [48].

iv) The important thing is not the consistory clause or the claims of the priority document, but whether the disclosure as a whole is enabling and directly and unambiguously gives the skilled person what is in the claim whose priority is in question. It must "give" this disclosure directly and unambiguously. It is not sufficient that it may be an obvious development from what is disclosed; *Abbot Laboratories Ltd v Evysio Medical Devices plc* [2008] EWHC 800 at [228].

v) Plausibility, as part of the requirement of an enabling disclosure, applies to issues of priority as well as sufficiency; *Hospira UK Ltd v Genentech Inc* [2014] EWCH 1094 at [149].

115. There was a dispute between the parties as to the legal effect of G 2/98. First, relying on the proposition that entitlement to priority is a matter of substance and not form, Cubist suggests that the question is whether "the same crux of the invention" or the "key concept" is disclosed in the priority document (Cubist's written closing submissions [273]-[274] and [283]). Secondly, relying on [8.4] of G 2/98, Cubist submits that when a dosage range is disclosed, there is disclosure of a sub-range within that range. Therefore, any selection of a sub-range is entitled to priority unless it constitutes a selection invention over the disclosure of the priority document. In order to assess these submissions, a more detailed analysis of G 2/98 is required.

116. In G 2/98 the President of the EPO, pursuant to Article 112(1)(b) EPC referred (amongst other questions) the following point of law to the Enlarged Board of Appeal:

> "1a) Does the requirement of the "same invention" in Article 87(1) EPC mean that the extent of the right to priority derivable from a priority application for a later application is determined by, and at the same time limited to, what is at least implicitly disclosed in the priority application?
>
> 1b) Or can a lesser degree of correspondence between the priority application and the subject-matter claimed in the later application be sufficient in this respect and still justify a right to priority?"

117. The reason for referring this question was because of conflicting decisions of the boards of appeal in relation to the scope of the right to claim priority, as explained in section II of G 2/98. Traditionally the scope of the right to claim priority from a previous first application had been regarded by the EPO as determined by, and limited to, the extent to which the subject-matter claimed in the later application had been at

least implicitly disclosed in the first application. However, in decision T 73/88 *Snackfood/HOWARD* (OJ EPO 1992 557), which had been followed by certain other boards of appeal, priority for a claim had been recognised, even though it contained an additional technical feature which had not been disclosed in the priority application. This was because the board considered that the feature in question was not related to the functional effect, and hence to the character and nature of the invention. Thus, its absence from the disclosure of the priority document did not cause loss of priority, provided that the claim was otherwise in substance in respect of the same invention as that disclosed in the priority document. The Board of Appeal in *Snackfood/HOWARD* held that a technical feature which was an essential feature for the purpose of determining the scope of protection was not necessarily an essential feature for the purpose of determining priority.

118. The Enlarged Board of Appeal rejected the *Snackfood/Howard* approach, which it characterised as "an extensive or broad interpretation of the concept of "the same invention"", and rejected the proposition that a distinction should be made between technical features which are related to the function and effect of the invention and technical features which are not, with the possible consequence that the claimed invention is considered to remain the same even though a feature is modified or deleted, or a further feature is added. Rather, it adopted "a narrow or strict interpretation of the concept of "the same invention""; [9]. Therefore, the Enlarged Board of Appeal answered the question referred to it as follows:

> "The requirement for claiming priority of "the same invention", referred to in Article 87(1) EPC, means that priority of a previous application in respect of the 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".

119. At [8] of its decision the Enlarged Board of Appeal explained why a narrow or strict interpretation of "same invention" was necessary to ensure a proper exercise of priority rights in conformity with the principles of equal treatment of the applicant and third parties, legal certainty and the assessment of novelty and inventive step. Essentially a broad interpretation, which allowed the addition, modification or deletion of "inessential features", would permit an applicant who had not disclosed an invention in a priority document to claim priority to the detriment of another applicant who had disclosed that same subject matter in a later priority document. Furthermore, there were no objective criteria for distinguishing between technical features which were related to the function and effect of the invention and technical features which were not.

120. In the context of explaining why a narrow, strict interpretation of "same invention" should be adopted, the Enlarged Board of Appeal stated at [8.4]:

> "If the invention claimed in a later European patent application constitutes a so-called selection invention - i.e. typically, the choice of individual entities from larger groups or of sub- ranges from broader ranges of numerical values - in respect of the subject matter disclosed in the first application whose priority is claimed, the criteria applied by

> the EPO with a view to assessing novelty of selection invention over the prior art must also be considered carefully when assessing whether the claim in the European patent application is in respect of the same invention as the priority application within the meaning of Article 87(1) EPC. Otherwise, patent protection for selection inventions, in particular in the field of chemistry, could be seriously prejudiced if these criteria were not thoroughly complied with when assessing priority claims in respect of selection inventions. Hence, such priority claims should not be acknowledged if the selection inventions in question are considered "novel" according to these criteria."

121. The Enlarged Board of Appeal was emphasising that where, for example, a priority document discloses a Markush formula which includes many compounds, a claim to one such compound would not be entitled to priority where the selection of the compound was considered novel. Therefore, if a selection invention was made after the priority document had been filed, it cannot claim the earlier priority. Otherwise, patent protection for a subsequent applicant who had disclosed the selection invention in his priority document could be prejudiced.

122. The Enlarged Board of Appeal did not say that where no selection invention is made, priority can *necessarily* be claimed for a particular sub-range, not disclosed in the priority document, on the basis of disclosure of a wide range. That conclusion runs contrary to the strict, narrow interpretation which the Enlarged Board of Appeal adopted of "same invention", and contrary to the policy considerations which it set out in section 8. The test in each case is whether the skilled person can derive the subject matter of the claim directly and unambiguously, using common general knowledge, from the priority document as a whole.

123. Therefore, I reject Cubist's submission that "same invention" within the meaning of Article 87(1) is to be determined by asking whether "the same crux of the invention" or the "key concept", is disclosed in the priority document. Further, I reject Cubist's submission that any selection of a sub-range is necessarily entitled to priority unless it constitutes a selection invention over the disclosure of the priority document.

Disclosure of the first priority document

124. The first priority document is short and simple. It discloses in its first paragraph that daptomycin is a novel anti-infective agent with potent activity against all gram-positive bacteria. It states that the compound has demonstrated safety and efficacy in Phase II clinical trials, and is currently being developed in both intravenous and oral formulations to treat infections in hospitalised patients caused by bacteria, including, but not limited to, methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant enterococci (VRE). It does not disclose any dosage regimen for these clinical trials.

125. The toxicity of daptomycin is then considered by reference to toxicology studies in animals. The first priority document states that:

> "Muscle toxicity was investigated most thoroughly in dogs, where it was found that repeated daily intravenous administration of high doses of daptomycin caused a pattern of acute degenerative and regenerative

> myopathy in the skeletal muscle. Muscle toxicity was dose-related in both incidence and severity, as shown in the table below."

126. The table referred to in that passage shows that:

i) Muscle myopathy was not observed at doses of 5 mg/kg/day

ii) Minimal to slight myopathy with low to moderate incidence was observed with doses of 10-40 mg/kg/day

iii) Slight to moderate myopathy with moderate to high incidence was observed with doses of 75 mg/kg/day

127. The first priority document also discloses that serum levels of CPK appeared to be a sensitive indicator of muscle toxicity in dogs, and that following doses of 40 and 75 mg/kg daptomycin, CPK activity in dogs increased within one week of treatment and peaked after two weeks of treatment. Increases reached up to 15 times pre-treatment values at these dose levels. Elevations of two to threefold were noted at dose levels of 20 and 25 mg/kg/day.

128. The first priority document records that a similar form of muscle toxicity was identified in a study of the effects of daptomycin on healthy human subjects. It states that two of five subjects who received daptomycin intravenously at a dose of 4 mg/kg every 12 hours experienced transient muscle weakness and pain of the forearms after 6 or 11 days of treatment. It discloses that treatment was discontinued 3 to 4 days after the initial elevation in CPK was noticed, and 1-2 days thereafter, CPK levels peaked at levels in excess of 10,000 U/L in one subject and 20,812 U/L in the second subject. It states the clinical symptoms and CPK increases subsided within several days after discontinuance of daptomycin administration, and the results of this study identified muscle damage as the dose limiting toxicity of daptomycin in humans.

129. There follows a section entitled "Further Experiments in Dogs" which discloses a study in which 75 mg/kg of daptomycin given once a day was compared with 25 mg/kg 3 times a day. The first priority document discloses that the three times a day dose regime was more toxic than the once-a-day regime. It also states that in a second study, a dose of 5 mg/kg administered three times a day caused muscle toxicity (measured by CPK) whereas this dose would be predicted to have no effect based on previous studies.

130. The first priority document reaches the following conclusion from these experiments:

> "The results of these new experiments indicate that the frequency of administration is an important variable in determining the muscle toxicity of daptomycin. Rather than being strictly related to the dose level (or the corresponding serum drug level), the degree of muscle damage appears to be related to the time between treatments. Muscle toxicity could be reduced by administering the drug in larger, less frequent doses, rather than small, frequent doses. It is possible that a certain interval between treatments is necessary for the repair of acute muscle damage. This is an unexpected conclusion that would not be anticipated on the basis of prior toxicology data."

131. Under the heading "Implications for Clinical Dosing", the first priority document concludes that longer intervals between doses of daptomycin (i.e. once every 12 hours to 24 hours) will minimise the possibility of muscle toxicity in the clinical setting and may permit the use of higher doses than have been possible so far. It refers to one embodiment of the invention where daptomycin is administered in a patient at a dose between 2-10 mg/kg at intervals between 12 and 24 hours. This is reflected in the single claim of the priority document which is as follows:

> "1. A method for the reducing muscle toxicity of daptomycin comprising the steps of administering to a patient in need of such therapy a therapeutically effective amount of daptomycin at a dose of 2-10 mg/kg of daptomycin and re-administering the same dose at intervals of between 12 and 24 hours.

132. There is no disclosure in the first priority document of administration of daptomycin of a dose between 3-10 mg/kg. There is no disclosure of administration of a dose of 3 mg/kg. There is no disclosure of the administration of the 2-10 mg/kg dose once every 24 hours (as distinct from a disclosure of administration at intervals of between 12 and 24 hours). There is no teaching in the first priority document that a dose of daptomycin once-daily will minimise muscle toxicity, whereas twice daily will not. It follows that there is no disclosure of the combination of 3-10 mg/kg once-daily.

133. I will now address the question of whether there is enough in the priority document to give the skilled person essentially the same information as forms the subject of proposed amended claim 1 of the 417 Patent and to enable him to work the invention in accordance with that claim. In my judgment, the answer is no. The differences between the dosing ranges and intervals disclosed in the 417 Patent and the first priority document result in a substantively different invention. The first priority document discloses daptomycin at a dose of 2-10 mg/kg administered at intervals between 12 and 24 hours will be efficacious and result in reduced toxicity. The invention of the 417 Patent as proposed to be amended is that the dosing interval must be 24 hours, not 12 hours and the dose must be, at minimum 3 mg/kg, not 2 mg/kg. Differences in the dose used is important to efficacy and toxicity, and, based on the dog studies in the first priority document, differences in the dosing interval are significant to toxicity, as Dr Harding accepted at T7/919/2-921/23.

134. I note that the Opposition Division held that the claimed dosage range of 3-10 mg/kg every 24 hours was not entitled to its priority claim based on the first priority document. At [3.2] of its decision the Opposition Division addressed the patentee's argument based on [8.4] of G 2/98. The argument, which was the same as that presented before me, was described as follows:

> "P argued that the claimed range of 3-10 mg/kg of claim 1 of the main request is not a novel selection over the range 2 to 10 mg/kg disclosed in P1. The two ranges are thus allegedly the "same invention" in the sense of G2/98 and consequently, P holds that the priority claim based on P1 is valid."

135. That argument was rejected by the Opposition Division for the following reasons:

> The OD, however, relies on a strict and narrow interpretation of the "same invention", which equates with "the same subject matter" (Rs 2 and 9, G 2/98). This approach requires that the subject matter of the claim (more specifically the feature 3-10 mg/kg) can be derived directly and unambiguously from P1 as a whole.

136. I agree with the reasoning of the Opposition Division. I have set out additional reasons which support the conclusion of the Opposition Division as to why the same invention is not disclosed in the first priority document as is claimed in proposed amended claim 1 of the 417 Patent.

137. I have also considered proposed amended claims 2 to 7, none of which in my judgment are entitled to priority. These claims simply provide more specific ranges or dosages within the same dosage interval as claim 1. In particular claim 2 seeks to disclaim 3 mg/kg; claim 3 claims specific doses 3, 4, 5, 6, 7, 8 or 9 mg/kg; and claims 4-7 claim specific doses 4 mg/kg, 6 mg/kg; 8 mg/kg and 10 mg/kg respectively, all to be administered once every 24 hours. None of these doses, to be administered once every 24 hours, is disclosed in the first priority document.

The second priority document

138. The second priority document is far more detailed than the first priority document. In particular, it expressly discloses the results of the two dog studies (A) and (B) that appear in Examples 1 and 2 of the 417 Patent. There is a general teaching in the second priority document, based on these dog studies, that once-daily dosing can minimise daptomycin muscle toxicity while optimising its antimicrobial efficacy. For example, the second priority document states at page 3 line 24 to page 4 line 4:

> "The results of Studies A and B suggest that the pharmacokinetic parameter defining daptomycin-associated skeletal muscle toxicity in dogs is not related to Cmax AUC or an intrinsically toxic plasma concentration, but is related to the dosing interval or percentage of time below particular plasma concentrations. Therefore, the data suggest that dosing interval had a greater influence on muscle toxicity than did dose itself. Further, studies in animal efficacy models have demonstrated that effectiveness of daptomycin is optimised by once-daily dosing because Cmax was found to be the key pharmacokinetic parameter associated with eradication of infection (J. Leggett et al., ICAAC abstract, 1987). These results suggest that once-daily dosing can minimise muscle toxicity, while optimizing its antimicrobial efficacy."

139. Furthermore, claim 4, which is part of the disclosure of the second priority document, claims a method according to claim 1, where daptomycin in a dose of 2 to 10 mg/kg is administered once every 24 hours. There is also express disclosure of doses of 3, 4, 5, 6, 7, 8 and 9 mg/kg doses in claim 3 and at page 5 lines 1-2.

140. Hospira points out, correctly, that nowhere in the second priority document is there an express literal disclosure of a range of 3-10 mg/kg once every 24 hours. However, this does not answer the question of whether there is enough in the second priority document to give the skilled person essentially the same information as forms the

subject of proposed amended claim 1 of the 417 Patent and enables him to work the invention in accordance with that claim. In my judgment, the answer to this question is yes. The differences between the dosing ranges and intervals disclosed in the 417 Patent and the second priority document do not result in a substantively different invention. The second priority document clearly teaches that that once-daily dosing of daptomycin can minimise muscle toxicity while optimising its antimicrobial efficacy. That general teaching, combined with the disclosure of the dosage range of 2-10 mg/kg, and specific doses of 3-9 mg/kg, is sufficient to disclose the same invention.

141. I note that the Opposition Division reached the same conclusion as to entitlement to priority based on the second priority document.

The Cubist Press Release

Disclosure

142. The Cubist Press Release can be relied on for anticipation and obviousness in the light of my finding that the 417 Patent is not entitled to its first claimed priority date. It describes a number of Phase II and Phase III trials being carried out for daptomycin for treating serious life-threatening infections.

143. The Cubist Press Release states that daptomycin has the advantage of rapid bactericidal activity and effectiveness in vitro against all gram-positive bacterial strains, including drug resistant strains. It states that:

> "Daptomycin exhibited a favourable side-effect profile in clinical trials completed to date and will be administered as a once-a-day therapy."

144. The Cubist Press Release announces that Cubist will be conducting the following daptomycin clinical trials:

i) An open label Phase II trial to evaluate three dosage regimens of daptomycin in treating bloodstream infections unassociated with endocarditis, in which daptomycin is dosed at levels of 4 mg/kg and 6 mg/kg administered intravenously once every 24 hours. This trial will be compared with a 3 mg/kg every 12 hour regimen used in a previous Phase II study.

ii) Two Phase III trials for complicated skin and soft tissue infections, each enrolling 400 patients. In each of the Phase III trials, 200 patients will receive 4 mg/kg of daptomycin intravenously once every 24 hours for up to 14 days.

Anticipation by the Cubist Press Release

145. As was made clear by Lord Hoffmann in *Synthon BV v SmithKline Beecham* plc [2006] RPC 10 at [19]-[33], for prior art to deprive a patent of novelty, two requirements must be met:

i) The prior art must disclose subject matter which, if performed, would necessarily result in infringement of the patent; *Synthon* at [22].

ii) The skilled addressee must be able to perform the claimed invention by using the matter disclosed in the prior art, read and understood together with his

common general knowledge. The test for enablement is the same as in the context of sufficiency; *Synthon* at [26]-[32].

146. Furthermore, if a claim comprises a particular technical effect, then that therapeutic effect is a functional technical feature of the claim and must be taken into account when assessing its novelty. *Regeneron Pharmaceuticals Inc & Bayer Pharma AG v Genentech Inc* [2013] EWCA Civ 93; [2013] RPC 28 at [56]; T-609/02 *Salk*.

147. In *Hospira v Genentech* [2015] EWHC 1796 Arnold J considered the novelty of functional technical features in the context of Swiss form claims and said at [59]:

> "…such claims are generally regarded as novel over a mere proposal to administer the drug to patients in the manner claimed. This is because the mere proposal does not disclose that the treatment is indeed efficacious. If it was obvious that the treatment would be efficacious, or at least it was obvious to conduct a trial of the treatment which would involve treating patients, then the claim is likely to lack inventive step but that is another matter."

148. Hospira submits that the Cubist Press Release anticipates the 417 Patent since there is a clear and unambiguous disclosure of the use of 4 mg/kg per 24 hours in a Phase III trial for complicated skin and soft tissue infections and the use of 4 mg/kg and 6 mg/kg per 24 hours to treat bloodstream infections. It submits that the requirement for disclosure of efficacy is met, because the fact that the Phase III trials are taking place indicates that efficacy must have been demonstrated in Phase II trials. In my view, this point is relevant to obviousness, but is not sufficient to establish anticipation.

149. I do not accept that the Cubist Press Release discloses that the treatments that it proposes are efficacious. Its treatment proposals are essentially forward-looking and do not state that clinical trials according to the proposed dosage regimens have actually taken place. Therefore, applying the case law set out above, I do not consider that the Cubist Press Release anticipates any of the claims of the 417 Patent.

Obviousness in light of the Cubist Press Release

Legal principles

150. Legal principles of relevance to the present case are as follows:

i) Obviousness must be considered on the facts of each case and the Court must consider the weight to be attached to particular facts in the light of all the relevant circumstances. These include the motive to find a solution to the problem that the patent addresses, the number and extent of possible avenues of research and the effort involved in pursuing them; *Generics (UK) Ltd v H Lundbeck AS* [2007] RPC 32 per Kitchin J, approved by the House of Lords in *Conor Medsystems Inc v. Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] 4 All ER 621, [2008] RPC 28 at [42].

ii) If a particular step is obvious in the light of the prior art, it is not rendered any less obvious merely because there are a number, and perhaps a large number,

of other obvious routes as well; *Brugger v Medicaid (No.2)* [1996] RPC 635 at 661.

iii) If the patentee chooses to advance broad claims, the inventive concept will be broadened in an equivalent way. The question to be answered is whether anything falling within the scope of the claims is obvious; *Brugger* (supra) at 656-657.

iv) Where it is alleged that a step is obvious to try, the question is whether the skilled person would do so with a fair expectation of success; how much expectation depends on the particular facts of the case. Including something in a research project is not enough to establish lack of inventive step; *Conor v Angiotech* at [42]; *Medimmune v Novartis* at [90]-[91]; *Teva UK Ltd v LEO Pharma AS* [2015] EWCA Civ 779 at [32].

151. In respect of the Lilly trials, Mr Waugh QC stresses the importance that such secondary evidence may have as an answer to obviousness. He draws attention to the following passage from the judgment of Jacob LJ in *Rockwater v Technip* [2004] EWCA Civ 381 at [123]:

> "123…All the "bits and pieces" of the invention were known separately for many years. The question "why was it not done before" is always a powerful consideration when considering obviousness, particularly when all the components of a combination have been long and widely known. Sometimes there is a good answer (e.g., no demand, not worth the expense, prior art only recent)."

152. Jacob LJ returned to this question in *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819; [2010] RPC 33 at [77], where he explained the "important role" that secondary evidence may play:

> "77. It generally only comes into play when one is considering the question "if it was obvious, why was it not done before?" That question itself can have many answers showing it was nothing to do with the invention, for instance that the prior art said to make the invention obvious was only published shortly before the date of the patent, or that the practical implementation of the patent required other technical developments. But once all other reasons have been discounted and the problem is shown to have been long-standing and solved by the invention, secondary evidence can and often does, play an important role. If a useful development was, in hindsight, seemingly obvious for years and the apparently straightforward technical step from the prior art simply was not taken, then there is likely to have been an invention."

Application to the facts

153. I have found that the Cubist Press Release clearly discloses the use of 4mg/kg per 24 hours in a Phase III trial for complicated skin and soft tissue infections and the use of 4 mg/kg and 6 mg/kg per 24 hours to treat bloodstream infections. Accordingly, dosage regimens falling within claims 1-5 are disclosed by the Cubist Press Release.

154. The issue in relation to obviousness of these claims is whether the skilled team would consider that the proposed clinical trials would have a fair expectation of success in demonstrating efficacy. Cubist submits that this question should be answered in the negative. It contends that the Cubist Press Release indicates no more than that Cubist was proposing to start clinical trials. The skilled person would know that Lilly's clinical trials had failed. Therefore, in the absence of data, it would be mere speculation as to whether Cubist's clinical trials would succeed.

155. Additionally, Cubist submits that the obvious thing for the skilled team to do in the light of the Cubist Press Release would have been to wait for the results of the clinical trials, rather than to take any action of its own.

156. I do not accept Cubist's submissions on this issue, for the following reasons. First, the skilled team would know from the announcement that the Phase III trials were to take place, and that the IND had been approved by the FDA, that efficacy must have been demonstrated in Phase II trials at doses which were sufficiently safe to proceed to Phase III trials.

157. In his written evidence Dr Harding suggested that the skilled person would not assume that Phase II trials had been done before the Phase III skin and soft tissue trial was to be carried out. However, during his cross-examination he accepted that the skilled person would assume that Cubist had appropriate efficacy and safety data to justify the Phase III trial and that it was supported by Phase II work; see T7/922/23-924/21, and in particular the following passage, which is of itself sufficient to establish a fair prospect of success:

> "Q. Right, and although it does not say specifically what support they have for the Phase III trials, they must have done or had in hand Phase II work to support doing the Phase III trial?
>
> A. Yes, you would anticipate they have some or they may have been able to re-analyse what Lilly did and discuss that with the FDA and get approval. I really cannot say from looking at this. But what it means is that the FDA has accepted that they can do these studies.
>
> Q. Yes, and therefore the reader of this would think first of all that daptomycin is very well worth taking forward for these indications and in these doses?
>
> A. They would assume so, yes.
>
> Q. That that is supported by Phase II work?
>
> A. Yes."

158. Secondly Dr Harding accepted that a company carrying out a Phase III trial would think that there would be a very good prospect of success because otherwise they would not have invested the considerable amounts of money which such a trial would require; (T7/924/22-925/2; 926/10-18). In my judgment, the skilled team would be well aware of this when reading the Cubist Press Release.

159. Thirdly, Dr Ebert's evidence was that the skilled reader of the Cubist Press Release would understand that the 4 mg/kg once every 24 hours dosing regimen must have been supported by enough data to justify the Phase III trial; Ebert (1) [7.9] & [8.22]. His view was that the skilled team would have a strong expectation on this basis that the stated doses and dosing intervals would be effective; [8.23]. I accept his evidence on this issue.

160. Fourthly, I have not accepted Cubist's case that the skilled team would know from its common general knowledge and from a literature search that Lilly's clinical trials had failed. I have found that the skilled team would discover from a literature search that Lilly's clinical trials had been successful in treating some gram-positive infections, including skin and soft tissue infections, bacteraemia and certain strains of endocarditis. Given that the Cubist Press Release announces trials in respect of bloodstream, skin and soft tissue infections, this knowledge would, if anything, increase the skilled team's expectation of success.

161. Fifthly, none of the claims of the 417 Patent are limited to the treatment of *S. aureus* endocarditis. Therefore, it is sufficient for Hospira to show that the claimed dosage regimen for daptomycin was obvious in respect of the treatment of any of bacteraemia, skin or soft tissue infections, to which the Cubist trials were directed.

162. Sixthly, I do not accept that it is an answer to obviousness to suggest that the skilled team would not be motivated to carry out its own trials as they would wait to see the Cubist trial results. Since the Cubist Press Release discloses the claimed dosage regimen of the 417 Patent, and gives to the skilled team a fair expectation that this will be efficacious to treat the infections as the subject of the clinical trials, the suggestion that the skilled team would choose to save its money until it saw the results is irrelevant to technical obviousness. In any event, this argument failed on the facts. Dr Ebert explained that the skilled team would be interested in participating in what had been announced as a multi-centre trial; T8/1156/11-24. Therefore, the argument that the only obvious course was to wait and see is incorrect.

163. Cubist submits that claims 6 and 7 are independently valid over the Cubist Press Release since paediatric dosing could not be determined until adult dosing was shown to be safe and effective, and could not be determined without pharmacokinetic tests. I do not accept this argument. I have found that it was common general knowledge that paediatric doses should be generally higher than adult doses. Dr Ebert has shown in Annex 1 to his first report why applying the paediatric equation, which was common general knowledge, results in doses which span 8mg/kg and 10mg/kg, depending on the weight and age of the child.

164. For these reasons, I have reached the clear conclusion that all of the claims of the 417 Patent lack inventive step over the Cubist Press Release.

165. Given my findings concerning lack of entitlement to the first priority date and obviousness over the Cubist Press Release, it is strictly unnecessary for me to determine the other objections to validity of the 417 Patent. However, in case I am wrong, I will proceed to consider the further grounds of invalidity.

Woodworth

Disclosure

166. Woodworth is a Lilly paper published in 1992. It is a Phase I study which examines the antibacterial activity, disposition and pharmacokinetics of daptomycin in healthy volunteers by conducting three separate single-dose studies, administering daptomycin intravenously at doses between 0.5 and 6 mg/kg.

167. The Abstract in Woodworth concludes that:

> "Daptomycin demonstrated in vivo antibacterial activity against all three test strains [methicillin-susceptible S. aureus ATCC2679, methicillin-resistant S. aureus or E. faecalis 3123], with the greatest activity observed against methicillin-resistant S. aureus. The predicted MIC for all three strains was approximately 13 µg/ml, corresponding to total (bound plus unbound) drug. On the basis of the drug's pharmacokinetics and antibacterial activity, doses of 4 to 6 mg/kg/day, possibly in divided doses, are predicted to be effective."

168. The introduction of Woodworth explains that daptomycin is active against aerobic, facultative and anaerobic gram-positive bacteria, including methicillin-resistant staphylococci and enterococci, and that initial studies in animals indicated that the compound is safe at doses which are effective in treating infection.

169. The details of the three studies reported in Woodworth are as follows:

i) In study A, a single 1 mg/kg dose of radio-labelled C-daptomycin was administered to healthy volunteers to determine the disposition of the drug. Samples of plasma, urine, saliva and breath were taken at regular intervals during infusion and post infusion. The samples were then measured for C content.

ii) In study B, doses of 0.5, 1.0, 1.5 and 2.0 mg/kg were administered to six healthy volunteers. At least 72 hours separated each dose. Blood and urine samples were collected at regular intervals to determine the pharmacokinetic parameters of daptomycin reported in Table 2

iii) In study C, healthy volunteers were administered daptomycin in successive single doses of 2, 3, 4 and 6 mg/kg:

> "Six volunteers were administered daptomycin in successive single doses of 2, 3, 4 and 6 mg/kg. Each dose was given as a 30-min constant-rate infusion of daptomycin in 50 ml of a 5% glucose solution. At least 72 h separated each dose.
>
> Blood samples for daptomycin analysis were collected at 0 and 30 min following the beginning of infusion and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h post infusion."

170. The results of the studies are shown in figures 1-4 and tables 1-3. Figure 3 shows linearity of dose versus AUC between 0.5 and 6 mg/kg from studies B and C, and

Woodworth states that a similar linear relationship was present between Cmax values and doses. Figure 4 shows the mean plasma concentration versus time plots for all single doses administered in studies B and C. Figure 5 shows the correlation of antibacterial activity with mean daptomycin concentrations. Table 2 shows the PK parameters for daptomycin at doses of 0.5-6 mg/kg and table 3 shows the duration and maximum antibacterial activity from single doses of daptomycin between 2-6 mg/kg. Woodworth states that no adverse events were reported or observed during the course of the studies and that "all doses were well tolerated" (pp.319 and 321).

171. Woodworth states that daptomycin demonstrated antibacterial activity in previously published in vitro studies (p.319). The discussion section in Woodworth describes the high protein binding of daptomycin and its relationship with antibacterial activity (p.324). It states that "free (unbound) daptomycin is present in concentrations which do provide at least 6 hours of antibacterial activity in serum from single 4 and 6 mg/kg doses".

172. The discussion section also refers to the antibacterial activity of daptomycin being predicted to last 8-10 hours after a single 4 mg/kg dose and 14-20 hours after a single 6 mg/kg dose. It explains that this is estimated on the basis of an assumption that daptomycin exhibits concentration independent killing, but that assumption is probably incorrect (i.e. daptomycin probably exhibits concentration dependent killing) and that a post antibiotic effect is also anticipated.

173. Based on study C, Woodworth concludes that "good antibacterial activity would be produced from single doses of 4 to 6 mg/kg." Woodworth further discloses that daptomycin could be administered once- or twice-daily due to its "longer half-life":

> "Most notable is the limited CLR [renal clearance] of daptomycin, with possibly safer use in renally impaired patients, and the drug's longer half-life, allowing once- or twice-daily administration with proper doses."

174. The last paragraph of the discussion states that:

> "our data suggest that good antibacterial activity would be produced from single doses of 4 to 6 mg/kg. However, the extended t½ of daptomycin predicts the accumulation of drug upon multiple dosing. Effective antibacterial activity may be produced by 2 to 3 mg/kg given every 12 hours, depending on the susceptibility of the organism."

175. Cubist submits that the Phase I studies in Woodworth disclose a dosage regimen for daptomycin at 2 to 3 mg/kg every 12 hours. It argues that there is no clear disclosure that daptomycin should be administered at a 24-hourly dosing interval as claimed in the 417 Patent. It submits that the statement in the abstract that "doses of 4 to 6 mg/kg/day" is not a disclosure of once-daily dosing. In particular, 4 mg per day does not state whether that should be with one 4 mg tablet once a day, or 2 x 2mg tablets taken twice a day or 4 x 1mg tablets taken 4 times a day.

176. I do not accept these submissions. In particular, the last sentence of the abstract and the last sentence of the penultimate paragraph of Woodworth clearly and unambiguously teach both 24 hourly and 12 hourly dosing as two options ("allowing

once- or twice-daily dosing…"). Woodworth clearly and unambiguously teaches a dosage regimen of 4-6 mg/kg of daptomycin once-daily, as well as a divided dose regimen. This is clear from the document, and was accepted by Dr Harding during his cross-examination at T7/905/14-18 and 911/4-12.

177. Cubist relies on the last paragraph of Woodworth to suggest that the authors were concerned about potential drug accumulation and therefore recommended a 12 hourly dosage interval, as opposed to 24 hours, in order to avoid this possibility. I do not accept this submission. Dr Ebert explained that the skilled person would understand the final paragraph, in the context of the whole disclosure of Woodworth, to mean that accumulation would be greater with shorter intervals so that lower doses should be given; T8/1144/2-13; but they would also understand that there would be less accumulation when dosing once every 24 hours, so a higher dose could be used; T8/1145/25-1146/19.

178. His view is confirmed by the teaching on p.324 of Woodworth that daptomycin at the levels tested (especially 6 mg/kg) would have anti-bacterial activity for the whole of a 24 hour period and by the statement in the penultimate paragraph, which expressly teaches that the longer half life of daptomycin (amongst other things) allows for once- or twice- daily administration with proper doses.

Anticipation by Woodworth

179. Cubist points out that Woodworth reports a Phase I study on 12 healthy patients. Phase II and or III studies, which would show the results of the administration of doses of daptomycin 24 hourly to patients suffering from infection, are not reported. Therefore, as with the Cubist Press Release, I do not consider that Woodworth clearly and unambiguously discloses that the dosage regimens that it reports are efficacious in the treatment of bacterial infections in humans. It does not anticipate any of the claims of the 417 Patent.

Obviousness in light of Woodworth

180. Cubist submits that the skilled team would not approach Woodworth in a vacuum. It claims that it would read Woodworth aware (whether from common general knowledge or a routine literature search) that: (a) Lilly had terminated its development of daptomycin; and (b) this was because of the unacceptable levels of toxicity during clinical trials. It points out that by the priority date, Woodworth was several years old, and submits that in the light of its knowledge of Lilly's failures, the skilled team would consider this document was of historical interest only. It also poses the question that if it was obvious in the light of Woodworth to adopt the dosage regimen claimed in the 417 Patent, why had Lilly not done this? Cubist submits that the published literature, such as Baltz, indicates that Lilly had not seen a way forward with daptomycin but instead had proceeded to look for analogues of daptomycin in the hope of finding a suitable antibiotic.

181. I do not accept these submissions for the following reasons. First, I have not accepted Cubist's case that the skilled team would know from its common general knowledge and/or from a literature search that Lilly's clinical trials had failed. I have found that the skilled team would discover from a literature search that Lilly's clinical trials had been successful in treating some gram-positive infections, including skin and soft

tissue infections, bacteraemia and certain strains of endocarditis. It would also discover that Lilly had not been able to treat *S. aureus* endocarditis successfully at the doses of daptomycin that had been administered, and it would know that this was the hardest infection to treat. It might be concerned about raising the total dose beyond 6 mg/kg but the available evidence indicated that daptomycin was safe and efficacious for infections other than *S. aureus* endocarditis up to this total daily dose.

182. Secondly, I have found that there is an answer as to why Lilly did not progress its development of daptomycin in the early 1990s:

i) Lilly had set itself the goal of treating a narrow sub-set of gram-positive infections with daptomycin, namely *S. aureus* endocarditis (which was the hardest nut to crack).

ii) For other gram-positive infections, including skin and soft tissue infections and bacteraemia, daptomycin had shown success during Lilly's clinical trials in terms of efficacy and had been well-tolerated up to 6 mg/kg per day.

iii) Even in relation to *S. aureus* endocarditis, there was only limited data that 4 mg/kg q. 12h (i.e. 8 mg/kg in total per day) had led to CPK elevations in 2 out of 5 patients and Lilly proposed further clinical trials to see if this represented a significant risk.

iv) Lilly were concerned that it would not be economically worthwhile to develop daptomycin unless its goal of treating *S. aureus* endocarditis could be achieved, given the market dominance of its vancomycin drug, and this contributed to its decision to terminate clinical trials on daptomycin.

183. Thirdly, I have found that by the priority date there had been an alarming increase in the amount of strains of pathogens that were resistant to antibiotics. This concern applied to all infections discussed in this case, including skin and soft tissue infections, bacteraemia and endocarditis. As compared to 1991/1992, by 1997/1998 there was a reason to re-assess potential treatments and new agents for treating resistant strains of gram-positive infections. Therefore, Woodworth would be read with interest at the priority date, having regard to this need.

184. Fourthly, Dr Ebert explained at [8.5]-[8.18] of his first report that, based on the pharmacokinetic and pharmacodynamic data in Woodworth; and the common general knowledge and the results of a routine literature search on daptomycin, the skilled team would expect that Woodworth's proposed dosage regimen of 4-6 mg/kg daptomycin once every 24 hours would be effective and well-tolerated. I accept this evidence. In summary, he explained that:

i) 4-6 mg/kg were shown in Woodworth to demonstrate effective antibacterial activity against various bacterial strains;

ii) Woodworth indicates that for all of the single doses administered, no adverse effects were seen and they were well-tolerated, so 4-6 mg/kg would be expected to be safe;

iii) Woodworth's suggestion that daptomycin exhibits concentration dependent killing would have informed the skilled person that, in order to maximise bactericidal activity it would be desirable to use a high Cmax less frequently;

iv) The half-life of daptomycin described in Woodworth would mean that the skilled person would understand that the drug would remain at effective concentrations for an extended period of time;

v) The reference to daptomycin having a PAE together with the teaching about the bactericidal activity lasting for 14-20 hours after a single 6 mg/kg dose would lead the skilled person to think that the daptomycin should stay at sufficient levels for 24 hours;

vi) The similarities between daptomycin and the aminoglycosides in respect of their pharmacokinetic and pharmacodynamic drivers for dosing purposes, together with knowledge that aminoglycosides could be and were administered once a day, would increase the skilled person's expectation of success.

I accept this evidence.

185. Fifthly, I have found that it was common general knowledge at the priority date that once-daily dosing is desirable, even where the patient is hospitalised, to maximise convenience, minimise the chances of missed doses and ensure clinical success. I have accepted Dr Ebert's evidence that if a once-daily dosing regimen had a similar efficacy and safety profile to a twice-daily dosing regimen, the skilled person would pursue the once-daily dosing regimen due to the practical benefits. This would have made Woodworth's proposal for a once-daily dosage regime of daptomycin particularly attractive at the priority date.

186. Sixthly, Cubist relies on publications of groups outside Lilly before the priority date, to question why, if the dosage regime of the 417 Patent was obvious, no-one else suggested it. This argument cannot succeed in the light of Woodworth, which explicitly discloses once-daily dosing at 4-6 mg/kg.

187. Finally, Cubist suggests that the obvious step, if anything, for the skilled team would have been to pursue a dosage regime of 2 mg/kg per 24 hours for daptomycin. This would require the skilled reader not to follow Woodworth's teaching that 4-6 mg/kg per 24 hours will be efficacious and well-tolerated. Furthermore, even if the skilled team began with that dosage regimen, there is no reason to believe that they would have stopped there, as Dr Ebert observed.

188. For these reasons, I conclude that claims 1-5 of the 417 Patent are obvious in the light of Woodworth. I also conclude that claims 6 and 7 are obvious, for the same reasons that I set out when considering obviousness over the Cubist Press Release.

Added matter/lack of clarity

Legal principles

189. The principles of relevance to this case may be summarised as follows:

i) The test of added matter is whether a skilled person would, upon looking at the amended specification, learn anything about the invention which he could not learn from the unamended specification; *Vector Corp v Glatt Air Techniques Limited* [2007] EWCA Civ 805; [2008] RPC 10 at [4], approving Jacob J in *Richardson-Vicks Inc's Patent* [1995] RPC 568 at 576.

ii) One reason for the rule against adding matter is that third parties should be able to look at the application and draw a conclusion as to the subject matter which is available for supporting the claimed monopoly. If subject matter is added subsequently, the patentee could obtain a different monopoly to that which the application originally justified; *AP Racing Ltd v Alcon Components Ltd* [2104] EWCA Civ 40; [2014] RPC 27 at [9]-[10].

iii) The test of whether the skilled person is confronted with new information depends on whether the combination of claimed features in the patent derives directly and unambiguously from the application, read as a whole. It is not necessary for the subject-matter of the amendment to have been explicitly disclosed in the application. Literal support is not required by Article 123(2) (T 667/08 of 20 April 2012, and the EPO Guidelines for Examination Part H, Chapter IV, §2.2).

iv) An intermediate generalisation occurs when "a feature is taken from a specific embodiment, stripped of its context and then introduced into the claim in circumstances where it would not be apparent to the skilled person that it has any general applicability to the invention"; *Nokia v IPCom* [2012] EWCA Civ 805; [2013] RPC 5 at [56].

v) The question is whether the feature in question would be seen by the skilled person as being generally applicable or only of significance in the context in which it was specifically disclosed; *Nokia v IPCom* at [59]-[60].

Application to the facts

190. Hospira contends that the application for the 417 Patent as filed does not clearly and unambiguously disclose the dosing regimen of 3-10 mg/kg once every 24 hours. Hospira observes in its written closing that the added matter argument is similar to the case of lack of priority over the second priority document. I agree with this observation, and I reject the added matter argument for the same reasons as I held that the 417 Patent was entitled to its second claimed priority date.

191. In particular, the application for the 417 Patent as filed contains dog studies A and B, as well as studies on patients. It clearly teaches that a once-daily dosage regimen of daptomycin minimises SMT, as compared with shorter dosing intervals. This is taught as a generally applicable feature, and not one which is only of significance in a specific context. Furthermore, it expressly discloses doses within the claimed range in the claims as proposed to be amended. For example, page 10 lines 14-15 state that:

> "In an even more preferred embodiment, daptomycin is administered in a dose of 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg/kg once every 24 hours."

192. Example 4 discloses that the administration of daptomycin to patients at a 4 mg/kg dose every 24 hours and at a 6 mg/kg dose every 24 hours did not cause an increase in serum CPK levels above the normal range, or in the very few patients who did experience such increase, the elevation was not considered to be related to daptomycin treatment.

193. Having regard to the application as filed, read as a whole, I do not consider that an amendment to a range of 3-10 mg/kg teaches the skilled person information relevant to the invention which he did not know from the application as filed.

194. Claim 2 requires that the dose range is from 3-10 mg/kg "but excluding 3 mg/kg". In my judgment, this exclusion has the effect that the claim is unclear as to what the lowest claimed dose is. It is unclear whether the lowest dose is, for example, 3.001 mg/kg, 4 mg/kg or one of the many other potential options between those values. I note that the Opposition Division held at [7.2] that, in respect of a claim containing this same exclusion, the requirements of Article 84 EPC were not met because the claimed range did not enable the skilled person to know where the range started. I agree with this reasoning.

195. Therefore, I reject the added matter objection but accept that proposed amended claim 2 would lack clarity.

Sufficiency – enablement across the full width of the claims

196. This objection was only advanced as a squeeze with the prior art. I do not accept it. The 417 Patent, with its reports of dog and human studies in Examples 1-2 and 4, renders it plausible that the dose regimen claimed will reduce skeletal muscle toxicity and the skilled team would expect from its common general knowledge that increasing the dose of daptomycin to the claimed range would increase its efficacy.

The Purity Patents

The witnesses in respect of the purity patents

Dr Baker

197. Hospira's expert in relation to the Purity Patents was Dr Simon Baker. Dr Baker is the Director of Global Research & Development for Bioline Reagents Limited, a company that manufactures proteins and reagents for molecular biology kits. Many of the materials produced by Bioline are produced by fermentation and then purified. He has a degree in microbiology from the University of Reading and a PhD from the University of Warwick in Biological Sciences, focussing on microbial physiology. In 1993 he was named a SERC Postdoctoral Research Assistant and BBSRC Postdoctoral Research Assistant at the University of Oxford. In that capacity, from 1993-1999 he conducted structural studies on the cytochrome cd1 nitrate reductase enzyme. This work included protein fermentation, purification and characterisation.

198. Dr Baker became a Lecturer in Microbiology at Birkbeck College in 2000, and a Senior Lecturer in Biotechnology at Oxford Brookes in 2006, where he remained until taking up his current position in 2012. Dr Baker gave evidence for Hospira in the US proceedings.

199. Mr Hinchliffe QC, who argued the case for Cubist in respect of the Purity Patents, suggested that:

i) Dr Baker's involvement in the US proceedings meant that his views of the prior art were tainted by his knowledge of the inventions in the Purity Patents.

ii) He had considerable personal experience of lipopeptides generally and surfactin in particular, which meant that he approached the Purity Patents with hindsight, or alternatively on the basis of experience far greater than that of the notional skilled person.

iii) He had been an academic for most of his career and was unable to see the issues in the same way as those who would have been looking to purify daptomycin at the priority date.

iv) Parts of the case put to Prof Myerson were not supported by Dr Baker.

v) Dr Baker had assumed that the skilled person had been instructed to purify daptomycin and had been provided with information about it. This illegitimately added a goal for the skilled person which would not have existed as a matter of common general knowledge at the priority date, and represented a change from his position in the US proceedings.

vi) Dr Baker introduced reasoning based on his personal knowledge that would not have been known to the skilled person.

vii) Dr Baker approached the case with the view that if a purification method was known and available, it was not inventive to apply it to the purification of any product, which was incorrect as a matter of law.

200. I do not accept any of these criticisms. I found Dr Baker to be a knowledgeable and fair witness. He had direct experience of purifying lipopeptides produced from fermentation at the priority date and experience of commercial purification work as a consultant. I reject the criticism that he was not entitled to give a different description of the skilled team from his evidence in the USA. He was entitled to re-address this question for the purpose of his UK reports, once the relevant concepts of the skilled addressee and common general knowledge under UK law had been explained to him.

Prof Myerson

201. Cubist's expert in relation to the Purity Patents was Prof Allan Myerson. Prof Myerson is Professor in the Practice of Chemical Engineering at MIT. He is a chemical engineer with particular interest in separation methods and purification processes used in the chemical, pharmaceutical and food industries. Over a long career, in his laboratory and as consultant to many companies, he has been involved in the purification of pharmaceutical products including antibiotics, polypeptides, glycosides and proteins. As with Dr Baker, I consider that Prof Myerson was a knowledgeable and fair witness.

202. Mr Meade QC on behalf of Hospira made the following observations about Prof Myerson's experience and the approach that he had taken the question of obviousness:

i) Prof Myerson had never worked on lipopeptides and was unable to comment on the views and experiences of those working on lipopeptides at the priority date. His evidence about the purification of lipopeptides was based on the literature that he had read for the purposes of this case.

ii) Prof Myerson was not an expert in fermentation and was not able to comment on Dr Baker's evidence in this area.

iii) Prof Myerson accepted that he had considered the question of obviousness over the prior art on the assumption that one of the differences between the claimed invention and the prior art was that the invention was an industrial scale process as to size and yield. However, there are no limitations in the claims as to size or yield.

203. In my judgment, these observations, whilst in no sense a criticism of Prof Myerson, are correct. I shall bear them in mind when considering the issues to which they relate.

Dr Kelleher

204. Dr Thomas Kelleher was a witness of fact called by Cubist. From 1999-2003 he was Senior Director of Marketing and Product Development at Cubist. He has a PhD in applied and industrial microbiology from Rutgers, the State University of New Jersey, and substantial experience in working in protein and peptide purification in industrial processes for various different companies. Dr Kelleher left Cubist in August 2003 and had no ongoing interaction with Cubist (with the exception of signing occasional patent-related or other legal documents) until 2013, when he became involved in the US proceedings in which he gave evidence for Cubist. I consider that Dr Kelleher was a fair and honest witness.

The skilled addressee

205. It was common ground that the skilled team would have an interest in, and experience of, purification processes. There were three areas of dispute between the parties:

i) Whether the skilled team would have experience of lipopeptides and an interest in purifying daptomycin.

ii) Whether a clinician would be included in the skilled team.

iii) The relevance of the scale of the purification processes.

Whether the skilled team would have experience of lipopeptides and an interest in purifying daptomycin

206. Dr Baker suggested that the skilled team would have an interest in purifying daptomycin, and previous experience of purifying lipopeptides in addition to proteins. Cubist criticised this approach on the basis that a definition of the skilled person which included a particular goal introduced hindsight into the analysis from the outset. As I have mentioned, it also pointed to Dr Baker's evidence in the United States where he did not suggest that the skilled person would have prior experience of lipopeptides or an interest in purifying daptomycin.

207. I do not accept Cubist's submissions on this issue, and I consider that the skilled team would have knowledge and experience of lipopeptides and an interest in purifying daptomycin for the following reasons. First, referring, for example, to the specification of the 179 Patent, the technical field of the invention is defined as "a process for preparing the highly purified form of the lipopeptide daptomycin". [0002] states that:

> "The rapid increase in the incidence of gram-positive infections – including those caused by antibiotic resistant bacteria – has sparked renewed interest in the development of novel classes of antibiotics. One such class is the lipopeptide antibiotics, which includes daptomycin."

It will be seen that the subject matter of the invention in which the skilled team has a practical interest is the purification of daptomycin. Furthermore, the Purity Patents acknowledge that at the priority date there was a renewed interest in the development of lipopeptides, including daptomycin. In my judgment, the skilled team would share that interest.

208. Secondly, and consistently with the disclosure of the Purity Patents, the experts were agreed that there was a real interest in 2000 in lipopeptides and biosurfactant lipopeptides in particular. Daptomycin was known by those working on lipopeptides as being an interesting antibiotic and Dr Baker, who was working on lipopeptides at the time was aware of daptomycin.

209. Thirdly, Dr Baker gave his evidence on the basis of a skilled person who was tasked with purifying daptomycin. Prof Myerson similarly addressed the issue of obviousness from the perspective of the skilled person who had been asked to purify daptomycin; Baker (1) [3.3]; Myerson (1) [27] and [132].

Whether a clinician would be included in the skilled team

210. I consider that the initial request for purified daptomycin would come from a clinician. Prof Myerson explained that clinical teams who had identified a clinical target would need to obtain it in purified form, and would ask a purification team to do this. Dr Zeckel confirmed that it would be routine for the clinical target to be identified and for the purification team to be tasked with purifying it. I find that by the priority date, the skilled team would have been aware of Cubist's interest in daptomycin. In particular Dr Harding and Dr Ebert indicated that by early 1999 it had become well known that Cubist was carrying daptomycin forward. Therefore, the wider skilled team, which would include a clinician, would have seen daptomycin as an interesting clinical target in 2000.

The relevance of the scale of the purification processes

211. Cubist submits that the principal focus of the Purification Patents is purification processes on a manufacturing scale, for commercial production. This is referred to in, for example, [0001], [0013] and [0016] of the 179 Patent. Cubist submits that this brings into consideration whether the separation would remain effective at a manufacturing scale and whether the overall yield/purity ratio would be adequate.

212. I do not agree. There was no dispute between the experts as to the various stages at which purification steps would need to be carried out. These included laboratory scale purification, in order to characterise the target of interest; pilot scale purification to prepare the target molecule for pre-clinical and clinical trials; and full commercial scale purification. None of the claims of the Purity Patents are limited to commercial scale purification and none specify any particular yield.

The 179 Patent

213. The 179 Patent is generally directed to a method of purification of daptomycin by the use of chromatographic steps with a "modified buffer". Claim 1 of the 179 Patent as granted is directed to a method of purifying daptomycin which includes binding the daptomycin preparation to an ion exchange resin in the presence of a modified buffer and one or more chaotropic agents, including urea. Claim 3 is similarly directed to a method of purifying daptomycin and includes the steps of subjecting a fermentation broth to (an)ion exchange chromatography ("AEC") to obtain an enriched daptomycin preparation; subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography ("HIC") to obtain a semi-purified daptomycin preparation; and subjecting the semi-purified daptomycin to modified buffer enhanced AEC, wherein the modified buffer is selected from a list of buffering agents and there is one or more chaotropic agents including urea.

214. There is a conditional application to amend claims 1 and 3 of the 179 Patent in the event that a particular added matter argument advanced by Hospira is successful.

The evidence of Dr Kelleher

215. Cubist relies heavily on the evidence of Dr Kelleher in answer to obviousness of the 179 Patent. It is convenient to summarise his evidence of relevance to the 179 Patent at this stage. I should emphasise that it was not suggested that the matters set out in Dr Kelleher's statements were common general knowledge, or indeed published. However, it was said by Cubist to constitute highly relevant secondary evidence, which showed that the obviousness attack was unrealistic and based on hindsight.

Dr Kelleher's first statement

216. At [18]-[23] of his first statement Dr Kelleher explained his understanding of Lilly's attempts to create clinical batches of daptomycin between 1984 and 1991. This was based on information that Dr Kelleher learnt at his time at Cubist and information from Lilly consultants to Cubist who were assisting in the technology transfer. In particular, he explained his understanding that Lilly had developed a method that supplied daptomycin for their investigational new drug ("IND") application and early phase clinical research. However, he understood that Lilly was unable to develop a purification method that would provide daptomycin at a yield and purity that would be viable for manufacturing. The average reported yield from more than 50 pilots and toxicology/clinical lots was about 1.9%. This approach could be used in a research environment but would not, in Dr Kelleher's view, result in a suitable manufacturing scale process with acceptable yields.

217. Dr Kelleher explained that although Cubist was not aware of the precise details of the process(es) used by Lilly to purify daptomycin, they understood that the clinical trials

material was purified using repeated HIC steps. His understanding was that this not only led to a low yield but only achieved purity of around 90 to 93%. The Lilly processes also resulted in an undesirable number of impurities and compositions that included endotoxins, which could cause fever in patients.

218. Dr Kelleher then set out initial work at Cubist to manufacture daptomycin for clinical trials by an ACN-based method similar, but not identical, to the methods used by Lilly. He recalled that there were various problems with daptomycin prepared by this method including low yields, high levels of endotoxins, too many impurities and low overall impurity. He discussed his work at Cubist from 1999 when he moved from his consultancy role to become an employee, with the goal of developing a viable manufacturing scale method. Cubist estimated that a viable manufacturing scale method would have to deliver yields of 25% or better with a purity that was greater than that reported by Lilly in their initial IND submissions to the FDA.

219. With this goal in mind, Cubist investigated methods of increasing fermentation output and looked into the effect of the decanoic acid addition rate on the production of daptomycin. It discovered that levels above 50 ppm were inhibiting the production of the microorganism and reducing the fermentation yield of daptomycin. Careful control of the decanoic acid feed at less than 50 ppm resulted in higher levels of daptomycin in the fermentation step.

220. Dr Kelleher then referred to the work done by Cubist to remove impurities in the broth, including, amongst other impurities, anhydro-daptomycin and β-isomer impurities. He referred at [45]-[46] to Lilly's understanding, contained in an extract from a laboratory notebook that he exhibited, that these impurities were in equilibrium with daptomycin. He explained that Dr Baker, a retired Lilly scientist and expert in daptomycin purification, told him that this equilibrium meant that daptomycin was not capable of being purified beyond 93 to 96%. Dr Baker's view was that the equilibrium caused the purity levels to return to below 93 to 96%, so further purification of daptomycin was not possible. Dr Kelleher said in his statement that this was a belief that seemed to be widely accepted by those who worked with daptomycin.

221. Dr Kelleher also explained that Cubist were told by Lilly that AEC could not be used to improve the removal of contaminants from daptomycin. This view was supported by Dr Baker, who maintained that HIC should be used to purify daptomycin and that Cubist should focus its efforts on optimising the process on the HP-20SS resin. However, Bill Downey, a chromatography specialist who was contracted by Cubist to investigate the daptomycin purification process, disagreed with this approach, as did Dr Kelleher himself. They did not think that HIC alone could lead to the 25% yield that they required and believed that AEC experiments were necessary.

222. In April 1999 Mr Downey reported the possibility of some separation of anhydro-daptomycin and later running impurities from daptomycin by AEC. However, the results were insufficient and the purities achieved were less than 88% with significant amounts of anhydro-daptomycin remaining in the samples. Therefore, Dr Kelleher contacted a company known as Perseptive Biosystems to discuss the possibility of working with them to identify chromatography conditions which would improve the purity of daptomycin. He was given contact details of Paul Lynch, who specialised in chromatography techniques.

223. Dr Kelleher contacted Paul Lynch in May 1999 and sent him daptomycin samples that were about 93% pure. Dr Kelleher suggested that AEC was worth considering as an option, but Paul Lynch was given general discretion to investigate chromatography methods. At this time, Mr Downey submitted a report setting out his opinion that it would be not be possible to separate daptomycin from its closely related impurities.

224. On 25 May 1999, a few weeks after he was first consulted, Paul Lynch presented results and recommendations to Cubist. In summary, Paul Lynch had noted through pH mapping that daptomycin displayed anomalous binding behaviour with an AEC resin. Binding was greater at low pHs. Higher pHs resulted in low resolution, such that closely running impurities could not be separated from daptomycin. Mr Lynch could see that there were broad peaks on the chromatogram at D3/7 p.90. Such peaks showed that there was no clear separation between daptomycin and its similarly structured impurities. He found that at pH 6 and 7, 6M urea dramatically reduced, if not eliminated, this binding and separated daptomycin from its impurities.

225. Dr Kelleher explained that, in collaboration with Paul Lynch, Cubist discovered that by using a modified buffer containing chaotropic agents, it could produce a step process on an AEC resin that removed daptomycin related impurities and resulted in a very high level of purity.

226. Dr Kelleher summarised Cubist's position at [68] of his first witness statement:

> "It became apparent that the widely shared view that the equilibrium between daptomycin and its impurities would prevent purification above a particular level was in fact a misconception. I consider that this misconception could have arisen for one of a number of reasons, for example, because Lilly had only used repeated HIC to purify daptomycin in the presence of aceto-nitrile, or because the Lilly process resulted in traces of catalytic species being present in the composition."

Dr Kelleher's cross-examination

227. Dr Kelleher's cross-examination emphasised some limitations on the evidence that he was able to give, certain of which were evident from his statement. First, he was unable to give direct evidence about what Lilly did in its purification work, or the reasons why these decisions were made, because he did not work for Lilly during the relevant period. No witness from Lilly was called by Cubist to explain its objectives, the steps that it took, or the reasons for such steps.

228. Secondly, Dr Kelleher was familiar with the use of AEC as an early purification step on frequent occasions in industrial protein and peptide purification, which explains why he was keen to use it for daptomycin; T3/248/14-24.

229. Thirdly, during his cross-examination, Dr Kelleher was shown an extract from a deposition of Mr Lynch from the US proceedings. This indicated that Mr Lynch, who had a Bachelor's degree in biology (but considerable experience in the industry), considered that when confronted with purifying a protein there was a standard set of steps that would have been followed to study its behaviour in 2000. The transcript

then records Mr Lynch's cross-examination concerning the approach from Dr Kelleher of Cubist in 1999:

> "Question: So Tom Kelleher from Cubist contacted you sometime before June 1999 to look into some optimisation and scale-up work for the daptomycin manufacturing process. Correct?
>
> Answer: Yes
>
> Question: And generally speaking, what you were tasked to do was use your standard approach that we discussed this morning to look at what chromatography techniques would be best suited for purifying daptomycin. Is that correct?
>
> Answer: Yes
>
> Question: And so based on your initial preliminary work on the daptomycin molecule, characterising it using the standard approach we discussed earlier, it was determined that pH range, salt, urea, temperature and loading were five factors to look into for further study. Is that correct?
>
> Answer: Yes
>
> Question: So is it fair to say then that based on screening the resins and optimising the pH variables, the specific resin used and the denaturant, you were able to come up with a process for purifying daptomycin?
>
> Answer: We came up with the best conditions with our products, yes.
>
> Question: Early this morning we talked about the standard approach that you adopted in determining purification methods for purifying proteins. Do you remember that?
>
> Answer: Yes
>
> Question: I understand that daptomycin is not a protein, but you didn't take a different approach to determining the purification method to purify daptomycin did you?
>
> Answer: No"

230. Cubist objected to the admissibility of this extract from Mr Lynch's deposition on the basis that it was not the subject of a Civil Evidence Act Notice in these proceedings. However, as with any other document, there was nothing to prevent Mr Meade from cross-examining Dr Kelleher about it, which he did.

231. Cubist's more substantial objection goes to the weight that I can attach to the extract from Mr Lynch's deposition. First, it is said that the extract which I have been shown has been edited by Hospira in that it was taken from a deposition of over 160 pages and is therefore inevitably selective. However, I was not shown any other passages from Mr Lynch's deposition by Cubist and there was nothing to suggest that the

passage which I have cited above was anything other than accurate. Secondly, it is submitted that as Mr Lynch is one of the inventors of the 417 Patent, his views as to whether process steps claimed in that document were standard are subjective and unreliable. Whilst this might be the case, I am unable to reach this conclusion, given that Mr Lynch was not called as a witness by Cubist. Thirdly, Cubist suggests that, had the extract from this deposition been the subject of a Civil Evidence Act Notice, then it would have considered whether to call Mr Lynch as a witness in these proceedings, in order to explain what he said in his deposition. I agree with Cubist that for this reason, the only evidential value of Mr Lynch's deposition is in the answers that Dr Kelleher gave to the questions asked of him.

232. Dr Kelleher was asked about the extract from Mr Lynch's deposition at T2/265 onwards. In particular, he was asked whether Mr Lynch had told him, when he presented his results in May 1999 that he had done anything non-standard in identifying aggregation as a potential problem and urea as a potential solution. Dr Kelleher did not recall specifically what was discussed at that meeting and made clear that Cubist did not know what Mr Lynch considered standard. Dr Kelleher said at T3/271/14-20:

> "A. From our point of view we did not know what he considered standard. There was proprietary information that Perseptive held. We did not lay out an experimental plan to him. We gave him the material and said, can you purify this. We also did not do a great deal of explaining to Paul Lynch that we had this equilibrium issue. We just let him go and see what he found."

233. So Mr Lynch was given very little guidance by Cubist, either as to the problem or solution. He came up with a solution within a few weeks and Cubist cannot present a positive case that he had any difficulty in working out the solution. Mr Lynch was a relevant witness, given Cubist's reliance on the development of its purification process, but he was not called to give evidence by Cubist.

234. Finally, Dr Kelleher's statement suggested that it was a widely held belief that because the anhydro-daptomycin and β-isomer impurities were in equilibrium with daptomycin, daptomycin could not be separated from these impurities and could not be purified above 93-96%. However, his cross-examination clarified that he only meant that this opinion was widely held within Lilly and that alleged purification limitations as a result of this equilibrium had not been published by Lilly; T3/257/19-258/4.

Common general knowledge of relevance to the 179 Patent

Purity versus yield

235. Prof Myerson explained, and I accept, that it was well known that purification processes developed in a laboratory on a small scale might not be suitable or practical on a manufacturing scale. Furthermore, there is a balance between levels of purity and yield in a full-scale commercial process and it might not be possible to achieve a very high percentage purity level whilst maintaining an acceptable yield. However, he accepted during cross-examination that the balance was different when dealing with laboratory or pilot scale processes and for smaller scale purification processes, a high

yield was less important. Since all of the claims include laboratory and pilot scale processes, if such processes are obvious, then so are the claims.

Fermentation and clarification

236. It was common general knowledge that naturally occurring molecules could be created by fermentation. Dr Baker explained (and Prof Myerson was not in a position to disagree) that it was well known at the priority date to use the technique of preferentially feeding the bacterium with nutrients which would favour the target molecule in question. In the case of daptomycin it was common general knowledge to create it by fermentation using a feed containing decanoic acid, at an appropriately low level to avoid toxicity. It was well known that solvents produced by fermentation would have to be clarified by standard methods in order to remove detritus.

Purification processes

237. Prof Myerson explained, and I accept, that there were a number of potential purification techniques which were available to the skilled person as a matter of common general knowledge. All of these, in my judgment, were standard techniques. These included chromatography, precipitation, crystallisation, liquid-liquid extraction, distillation, adsorption, membrane separation, ion-exchange, electrophoresis, filtration and centrifugation. He also explained, and I accept, that there were a number of chromatographic techniques that could be employed, which were well known. These included normal phase chromatography, reverse phase chromatography, ion exchange chromatography, hydrophilic interaction chromatography and hydrophobic interaction chromatography.

Multiple purification steps and modes

238. It was standard practice at the priority date to use multiple purification steps when purifying naturally occurring molecules produced by fermentation, due to the large number of impurities in a fermentation broth. Prof Myerson agreed that when purifying a biological molecule from fermentation the skilled person would not expect to be able to do this with just one chromatographic step; T5/566/6-18.

239. Furthermore, the experts were agreed that it was standard practice to use more than one mode of purification, because simply repeating the same mode of purification would target the same property of the molecule. For example, in the textbook, *Protein Purification, Principles, High-Resolution Methods and Applications,* Janson and Ryden, second edition (1998) it is stated that:

> "Normally, however, one has to combine several chromatographic methods to achieve complete purification of a protein from a crude biological extract. With the wide variety of chromatographic media available today, this can normally be done in a short period of time."

The experts were also agreed that the order in which the steps were performed could have an effect on the purity of the products produced.

AEC

240. AEC was a standard purification technique at the priority date. I accept the evidence of Dr Baker at [4.27] of his first report that:

> "Anion exchange chromatography was (and still is) the most commonly used purification technique because the buffers were readily available and easy to make up and use. I have never worked in a laboratory that did protein purification that did not have an ion exchange chromatography column, nor am I aware of having visited one."

241. In addition, it was common general knowledge at the priority date that AEC was useful as a first step in a chromatographic process as it combined concentration with purification. This was set out in a variety of textbooks on protein purification, for example Janson and Ryden (supra). Dr Baker explained, and I accept, that it was most common at the priority date to start with ion-exchange chromatography. Prof Myerson explained that chromatography was not the only choice for the first stage of purification but was one of three likely choices, and that AEC was a routine first step if the skilled person had chosen chromatography; T5/565-566; T5/572-573.

Purification techniques used on lipopeptides

242. Cubist submits that the standard way of purifying lipopeptides at the priority date was by the method described in an article by Cooper et al. published in Applied and Environmental Microbiology, September 1981, p.408-412. This involved the addition of HCl to precipitate the lipopeptide extract with dichloromethane and recrystallisation. This method was reported in a number of other papers published before the priority date. Cubist suggests that the skilled person who looked in the literature for purification methods for lipopeptides would have concluded that the Cooper method was the standard way to purify them. Although some chromatography had been used, it was mostly HIC. According to Cubist, the skilled person would have concluded that AEC had not previously been used to purify lipopeptides.

243. Cubist relies on the fact that Dr Baker gave evidence about a literature search which he expected that the skilled person would have done and exhibited to his first report the key papers that would have found and read. He was cross-examined about this at T/4/407-417 and it was pointed out that he had not found a published paper which used AEC to purify a lipopeptide.

244. However, Dr Baker's first report made clear at [4.34]-[4.35] that he considered AEC, as well as HIC, were "techniques applicable to purifying lipopeptides as much as they were to purifying proteins". Prof Myerson set out his view in his reply report that there were other purification strategies available for lipopeptides, as well as the chromatography methods referred to by Dr Baker, but he did not suggest that AEC was thought to be inapplicable to the purification of lipopeptides. During his cross-examination, it became clear that Prof Myerson did not support the view that anion exchange chromatography would not have been considered in respect of lipopeptides in general and daptomycin in particular; T5/523/18-524/9, and in particular:

> "A. In answer to your question, certainly one will consider all separation methods, including ion-exchange chromatography in looking to develop a separation method for a given compound.
>
> Q. Including daptomycin?
>
> A. Yes."

245. Prof Myerson accepted that AEC was a standard technique which would have been understood to apply to the purification of any molecule, not just proteins. Furthermore, Prof Myerson was shown during his cross-examination a number of examples of publications before the priority date where AEC was used to purify lipopeptides.

246. I accept that the Cooper method was one standard way of purifying lipopeptides at the priority date. I do not accept that the skilled team would have concluded that AEC should be not be used when purifying lipopeptides and that its use was confined to proteins. In my judgment the skilled team would have regarded AEC as a standard technique available for the purification of any molecule, including lipopeptides.

HIC and lipopeptides

247. It was common general knowledge at the priority date that HIC was a standard purification technique, and was referred to as such in, for example, Janson and Ryden in relation to protein purification. Furthermore, it was well known that this standard technique could be applied to lipopeptides and there were a number of examples of HIC being used, before the priority date, to purify lipopeptides; for example Desai and Banat *Microbial Production of Surfactants and Their Commercial Potential, Microbiology and Molecular Biology Reviews* (1997); *Lin et al Structural and Immunological Characterisation of a Biosurfactant Produced by Bacillus licheniformis JF-2* Applied and Environmental Microbiology (1994).

The use of AEC in combination with HIC

248. Prof Myerson was cross-examined on the basis of a product manual from 1998 for an anion exchange column marketed by a company known as Vydac. Under the heading "Why use ion-exchange chromatography to purify proteins?", the product manual states that:

> "Ion exchange chromatography is an excellent complement to such high-resolution techniques as reverse-phase chromatography."

Reverse-Phase chromatography is a subset of HIC.

249. Prof Myerson explained the technical reason why it was standard practice to use AEC and HIC together:

> "Q. And the reason techniques like this are considered complementary is because if you simply keep doing one step after another all focusing on charge, it very much limits what you can achieve.
>
> A. That is correct.

> Q. Whereas if you do one separation based on charge and then another one based on hydrophobicity, you are looking at two different characteristics of the molecule.
>
> A. That is correct.
>
> Q. And that gives you better results.
>
> A. It should."

250. Prof Myerson accepted that it was common general knowledge at the priority date to use AEC followed by HIC, to exclude the need for a separate de-salting step, and that it would have been common general knowledge that this could be applied to lipopeptides; T5/573/10-574/22.

251. Dr Baker explained that after HIC the skilled person would need to carry out a step to remove the solvent. AEC was a common general knowledge method to achieve that; T4/420/4-13. Prof Myerson agreed that the use of AEC after HIC to reduce the volume of the solvent and to further purify the solution was common general knowledge at the priority date. Prof Myerson was shown the use of an anion exchange step to reduce the solvent, after the HIC step, in the 417 Patent:

> "Q. And this use of the anion exchange column in that way is just exactly what is in the contemplation of the common general knowledge that we have been looking at over the last few minutes in those textbooks, is it not?
>
> A. In terms of the fact that the amount of solvent is reduced, I would agree.
>
> Q. And concomitantly, to use a word from one of those books, I think you would expect to get purification at the same time if you designed things adequately?
>
> A. If you did, that is correct."

252. Having considered the evidence of Dr Baker and Prof Myerson on this issue, I conclude that the sequence of chromatographic steps of (i) AEC; (ii) HIC; and (iii) AEC was a common general knowledge process of purification at the priority date, and the skilled team would have appreciated that it was potentially applicable to the purification of daptomycin.

The use of buffers and chaotropic agents

253. It was common ground between the experts that using buffers, including Tris, was standard practice.

254. As to chaotropic agents, the evidence established that urea was a standard addition to an AEC column in order to remove or avoid aggregation. Dr Baker explained this clearly during his cross-examination at T4/429/11-19:

> "A. …I would say that the use of chaotropic aggregations, particularly of the urea, it is so commonly known that I found it difficult to find a clear instance of it being used. It was referred to in this particular paper for the purposes of dissolving aggregates. The use of chaotropic agent to get rid of aggregates is common in protein purification, and urea is one of the oldest biological molecules known. It has been used for a very long time."

255. His evidence is confirmed by the references to the use of urea for this purpose in product manuals for chromatography columns before the priority date. For example, the Vydac manual (supra) refers to urea being used to avoid protein aggregation and refers to using urea and other chaotropic agents to break-up complexes.

256. Prof Myerson agreed that the use of urea was a well-known remedy to address aggregation; T5/611/25-612/8:

> "A. I believe that the use of chaotropic agents was common general knowledge and urea was a common chaotropic agent, so I would have to agree with that."

257. Prof Myerson agreed that when the results of a chromatographic step produces broad peaks, aggregation would be on the standard list of possible causes of those broad peaks, and the skilled person would carry out tests to see if it was aggregation or another cause. Prof Myerson also agreed that these would be standard tests that would not merit publication.

Daptomycin

258. Cubist submits that although the skilled team would recognise daptomycin as a lipopeptide if it was shown its structure, it would not be aware of daptomycin as a matter of common general knowledge from the outset. It points out that daptomycin does not appear in general reviews of lipopeptides or surfactants published prior to 2000.

259. I have dealt with this issue in the context of the skilled addressee of the Purification Patents. I have found that at the priority date, there was a real interest in lipopeptides and biosurfactant lipopeptides in particular. Daptomycin was known by those working on lipopeptides as being an interesting antibiotic and it was well known that Cubist were carrying daptomycin forward. I consider that the antibiotic daptomycin was common general knowledge at the priority date, and that it was a target of interest for purification.

Anhydro daptomycin and the β isomer of daptomycin

260. It was common ground that before embarking upon purification of a compound, it was important to establish from the literature what was known about the target and related compounds. A literature search at the priority date would reveal a paper by Kirsch et al., 1989, which identified two degradation products of daptomycin as anhydro-daptomycin and a β-asp isomer of daptomycin. The Kirsch paper suggested at p.3 that daptomycin might go into equilibrium with the anhydro-daptomycin and the β isomer. Cubist submits that, having read the Kirsch paper, the skilled team would form the

view that the existence of this equilibrium meant that it was not possible to separate daptomycin from anhydro-daptomycin and the β isomer and that this would limit the purity that it was possible to achieve with daptomycin.

261. I reject Cubist's submission on this issue for the following reasons. First, if the skilled team had formed this view, it would have been an incorrect technical prejudice, because it is common ground, and a fundamental premise of the 179 Patent, that it is possible to separate daptomycin from anhydro-daptomycin and the β isomer. The existence of any equilibrium does not limit the purity that can be achieved with daptomycin.

262. It is settled law that such a perceived technical prejudice or "lion in the path" must be a widely or universally held but incorrect opinion of a technical fact. It is not enough for it to be an opinion held by limited number of individuals: T 1989/08 at [4.3.1]. Pumfrey J explained this in Glaxo Group's Patent [2004] RPC 43 at [30]:

> "A technical prejudice must be general: it is not enough that some persons actually engaged in the art at the material time labour under a particular prejudice if a substantial number of others do not. A prejudice which is insufficiently widespread for it properly to be regarded as commonly shared will not, in my view, be attributed to the notional skilled person."

263. The suggestion that this technical prejudice existed was not made by Prof Myerson in his written reports. It was developed for the first time during the cross-examination of Dr Baker. Whilst the point is, of course, open to Cubist, if such a widespread technical prejudice existed, I would have expected to find it set out in Prof Myerson's evidence from the outset.

264. Secondly, Prof Myerson made clear during his cross-examination that the existence of such equilibrium depends upon the exact conditions and timing of the purification process; T5/586/5 – 587/10. As he said:

> "So it all depends on the conditions at which you prepare your solution. The time it takes and the rates of reaction compared to the equilibrium"

265. Dr Baker explained that the possible existence of an equilibrium would not lead the skilled person to assume that anhydro-daptomycin and the β isomer could not be separated from daptomycin as, in common with Prof Myerson, he considered that whether an equilibrium would be reached would depend upon the conditions and timing of the purification process; T4/434/21-435/10. He also pointed out that if it were the case that as soon as the impurities were separated the equilibrium would start to reform then there would be "a very fundamental problem with daptomycin." This is not a problem which the 179 Patent solves, as it only makes passing reference to Kirsch et al, and does not describe the equilibrium nor how the invention is said to avoid it; c.f. Jacob LJ in *Pozzoli SpA v BDMO SA* [2007] EWCA CIV; [2007] FSR 37 at [27]-[28].

266. Thirdly, Prof Myerson's evidence did not support the proposition that reforming of the equilibrium would be a real problem in practice. He explained that once the drug

was lyophilised then the solution-based reactions moving towards the reinstatement of the impurities would all stop. He made clear that the drug would be administered in a relatively short time after being made up for intravenous administration to avoid side products from forming; T5/587/11-588/17. Cubist submits that this is hindsight reasoning. I do not agree. The technical proposition was apparent to Prof Myerson.

267. Cubist also submits that this was contrary to the view of Lilly who lyophilised its product after chromatography but still thought that the equilibrium limited the possible purity levels achievable for daptomycin. Having heard the evidence of Dr Baker and Prof Myerson, I do not accept that, if this was Lilly's view, it would have been shared by the notional skilled team in the light of common general knowledge. I shall consider Lilly's development work further when addressing the alleged lack of inventive step of the 179 Patent.

The specification of the 179 Patent

268. The technical field of the invention is described as being a process for preparing a highly purified form of the lipopeptide daptomycin. [0002] describes the incidence of gram-positive infections and concerns about resistant bacteria. It refers to an increased interest in lipopeptide antibiotics including daptomycin. It states that daptomycin has potent bacterial activity in vitro.

269. Paragraph [0008] discusses US 843, which is cited as prior art in these proceedings. It explains that US 843:

    i) describes a daptomycin purification method in which the fermentation broth was filtered and passed through a column containing HP-20 resin. After elution the semi-purified daptomycin was passed through a column containing HP-20ss, and then separated again on HP-20 resin;

    ii) states that final resolution and separation of daptomycin from structurally similar compounds by this method is impeded by the presence of impurities that are not identifiable by ultraviolet analysis of the fermentation broth;

    iii) states that attempts to remove these impurities by reverse phase chromatography over silica gel, normal phase chromatography over silica gel or ion exchange chromatography also failed to significantly improve the purity of daptomycin;

    iv) discloses a "reverse method" for purification comprising particular steps;

    v) teaches that this method improves the final purity from about 80% to about 93% and increases the yield from about 5% to about 35%;

    vi) does not disclose the type of impurities present in the daptomycin preparation.

270. Paras [0009] – [0011] refer to US 5,912,226 and the Kirsch paper that reported the production of two impurities of daptomycin that were produced in the purification of daptomycin. These are anhydro-daptomycin and the β-isomer. Para [0012] notes that the 226 Patent reports how daptomycin may be produced so that the daptomycin contains no more than 2.5% of the β-isomer and anhydro-daptomycin.

271. Under the summary of the invention, para [0013] states that the invention provides commercially feasible methods to produce high levels of purity of daptomycin. It refers to embodiments being: commercially feasible methods for obtaining daptomycin at a purity level of 95-97%; commercially feasible methods that almost completely eliminate the major anhydro-daptomycin and β-isomer impurities; and commercially feasible methods of purifying daptomycin by forming micelles.

272. Paras [0016]-[0023] set out the objects of the invention. These include:

    i) to provide a process that can be easily scaled for commercial production and which comprises a unique combination of anion exchange chromatography and hydrophobic interaction chromatography. A preferred embodiment of this method produces daptomycin that is at least 95% pure and contains reduced levels of impurities compared to daptomycin produced by the prior art methods [0016];

    ii) to increase the levels of daptomycin produced by the fermentation by adding reduced amounts of decanoic acid into the fermentation [0017].

    iii) to disclose a method of purification of daptomycin by use of a modified buffer anion exchange chromatography [0018]. Para [0019] refers to including the modified buffer anion exchange chromatography in the last of the combination of steps referred to in para [0016];

    iv) to disclose a method of purifying daptomycin that is easily scaled for commercial production using micelles.

273. Paras [0024]-[0044] set out a number of definitions. Those of relevance are at [0030]-[0036]. In particular:

    i) "Substantially pure" daptomycin means at least 95% pure; "essentially pure" means at least 97% pure; [0030]-[0031].

    ii) Daptomycin is "substantially free of another impurity" when that other impurity is present in an amount of less than 1% of the daptomycin; "essentially free of another impurity" when the impurity is less than 0.5% and "free of another impurity" when the impurity is less than 0.1%; [0032]-[0034].

    iii) "Purified daptomycin" is either substantially pure or essentially pure daptomycin; or daptomycin that is substantially free, essentially free or free of another impurity; [0035].

    iv) "Partly purified daptomycin" is daptomycin that is less than 90% pure; [0036].

274. Paragraphs [0045]-[0102] describe in detail methods for manufacturing purified lipopeptides, starting with the process of fermentation of Streptomyces roseosporus to produce daptomycin. The first method comprises steps of anion exchange chromatography, HIC chromatography and further anion exchange chromatography; [0045]-[0061].

275. Paragraphs [0062]-[0066] describe a method of chromatography that is said to achieve a level of purity not achievable by the prior art methods. The 179 Patent

refers to this as modified buffer anion exchange chromatography. Para [0063] explains that partially purified daptomycin is further purified as follows:

i) Daptomycin is bound to anion exchange resin in the presence of an appropriate ionic modified buffer under conditions in which daptomycin binds to the resin ion in a monomeric and non-micellar state.

ii) The modified buffer comprises a buffering agent, such as, without limitation, acetate, phosphate, citrate and Tris-HCl, or any other buffering agent that buffers well at neutral pH.

iii) The modified buffer further comprises one or more chaotropic agents, including, without limitation, guanidine, ammonia, urea, a strong reducing agent, benzoate, ascorbate or another ionic enhancer capable of modifying the buffer so that daptomycin is easily separated from impurities.

iv) The daptomycin-loaded resin is washed with an appropriate ionic modified buffer to elute impurities, including anhydro-daptomycin.

v) Daptomycin is then eluted under conditions that permit the separation of daptomycin from impurities that remain bound to the resin, including the β-isomer.

276. Accordingly, the modified buffer includes a chaotroptic agent which prevents aggregation of the daptomycin and ensures that it binds to the resin in a monomeric, non-micellar state. The resin is then washed with the modified buffer. This elutes impurities, including anhydro-daptomycin. The daptomycin is then eluted from the resin under conditions that leave the β isomer bound to the resin. Thus the modified buffer anion exchange chromatography is said to permit the separation of daptomycin from anhydro-daptomycin and the β isomer.

277. Paras [0066]-[0073] explain that the modified buffer anion exchange chromatography can be used in combination with earlier anion exchange and reverse phase chromatography steps. These steps are said to produce daptomycin that is at least 98% pure.

278. Examples 1-6 concern modified buffer AEC. Dr Baker summarised their key aspects in a table, which I reproduce below. It will be seen that urea is used in all of these examples:

Example	Column	Buffer	Chaotropic agent	Wash	Elute	Purity
1	Poros 150 anion exchange resin	Tris pH 7.0	6M urea	30mM NaCl	~300mM NaCl	>99%
2	Poros D50 anion exchange resin	Acetate pH 7.0	6M urea	30mM NaCl	~300mM NaCl	96.92%
3	Poros D50 anion exchange resin	Tris pH 7.0	6M urea	Tris pH 7.0 and 6M urea	~300mM NaCl	98%
4	Poros D50 anion exchange resin	Acetate pH 7.0	6M urea	30mM NaCl	~300mM NaCl	98% - 99%
5	Poros 150 anion exchange resin	Acetate pH 6.0	2M urea	Same buffer	150 – 300 mM NaCl	99% - 99.5%
6	Poros 150 anion exchange resin	Acetate pH 6.0	2M urea	60mM NaCl in same buffer	250mM NaCl in same buffer	98.8% - 99.5%

279. Example 8 gives the details of analytical HPLC on a bulk daptomycin preparation before the modified buffer AEC process is applied to it. The bulk daptomycin is 90% pure and there are a substantial amount of impurities, in particular anhydro-daptomycin and the β isomer. After the modified buffer AEC process, the daptomycin is 99% pure and anhydro-daptomycin and the β isomer are not detectable; [0122].

The claims of the 179 Patent as granted

1. Claims 1, and 3 and 4 of the 179 Patent are set out below:

> 1. A method to purify daptomycin, comprising the steps of:
>
> (a) supplying a daptomycin preparation that contains at least 2.5% of a combined amount of anhydro-daptomycin and β-isomer of daptomycin;
>
> (b) binding the daptomycin preparation to an anion exchange resin in the presence of a modified buffer under conditions in which daptomycin binds to the anion exchange resin in a monomeric and non-micellar state, wherein the modified buffer comprises a buffering agent selected from acetate, phosphate, citrate and Tris-HCI and one or more chaotropic agents selected from ammonia, urea, benzoate and ascorbate;
>
> (c) washing the anion exchange resin in the presence of the modified buffer under conditions that elutes anhydro-daptomycin but retains daptomycin;

> (d) eluting daptomycin in the presence of the modified buffer under conditions that separate the purified daptomycin from the β-isomer of daptomycin; and
>
> (e) obtaining purified daptomycin.
>
> 3. A method to purify daptomycin, comprising the step of:
>
> (a) fermenting Streptomyces reseosporus with a feed of n-decanoic acid to produce daptomycin in a fermentation broth;
>
> (b) clarifying the fermentation broth;
>
> (c) subjecting the fermentation broth to anion exchange chromatography to obtain an enriched daptomycin preparation;
>
> (d) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and
>
> (e) subjecting the semi-purified daptomycin preparation to modified buffer enhanced anion chromatography, wherein the modified buffer comprises a buffering agent selected from acetate, phosphate, citrate and Tris-HCI and one or more chaotropic agents selected from ammonia urea, benzoate and ascorbate to obtain purified daptomycin.
>
> 4. The method according to claim 3, wherein the feed of n-decanoic acid in step a) is regulated to achieve a residual concentration of n-decanoic acid of no more than 50 parts per million (ppm) during fermentation; said clarifying in step b) comprises extracting the fermentation broth with a buffer comprising butanol; the anion exchange chromatography in step c) is performed on FP-DA 13 resin; or either or both steps c) or e) comprises the use of a continuous salt gradient or step salt gradient.

280. I do not need to set out claim 5, also alleged to be independently valid, as Cubist accepts that if claim 1 is obvious, then claim 5 will not add anything inventive to claim 3. Nor do I need, at this stage, to set out the conditional amendments to the claims, as they are only relied upon, if necessary, to overcome an added matter objection. Neither side suggested that they make any difference to the obviousness case.

281. As to claims 1 and 3, the following points are of relevance. First, neither of the claims require that the purification method is used at commercial levels, or to produce a particular yield. As Birss J said in *Hospira v Genentech* [2014] EWHC 1094 at [183]:

> "Just because the focus of the specification is on larger scale operations, that is not a reason to read limitations into the claims which are not there. The claims contain no language which the reader would

> think was an attempt to limit them to material made on any particular scale."

282. Secondly, although both claims 1 and 3 include AEC steps, there is a difference between them. In claim 1, the AEC step is performed on a daptomycin preparation with at least 2.5% combined anhydro-daptomycin and β isomer. There is no limitation as to when in a multi-step process this method is performed. Indeed, there is no reference in the claim to a multi-step process. In claim 3, the first AEC step is required to be carried out on the fermentation broth (and before the HIC step) whereas the second AEC step is required to be carried out after the HIC step.

The disclosure of US 843

283. US 843 states that the process it describes provides a novel method for the separation and purification of a wide variety of fermentation products, including LY146032 (which the skilled team would discover from a literature search was Lilly's designation for daptomycin), from their fermentation broths, or from "partially purified process streams", by use of a reverse phase non-functional resin.

284. US 843 explains that "semi-pure" daptomycin could previously be made by filtering the fermentation broth (i.e. clarifying it) and passing the filtrate through a column containing HP-20 resin, washing with water and water:acetonitrile, and eluting with water: acetonitrile. It explains in the prior art process, the semi-pure daptomycin was dissolved in a buffer and passed through a column containing HP-20ss resin (a version of the HP-20 resin with a smaller particle size). The purified fractions containing daptomycin obtained from this column were then diluted with water and loaded onto a column again containing HP-20 resin, washed with water and eluted with acetonitrile: water. According to US 843, these steps were repeated as often as possible to give a product of the desired purity.

285. US 843 then explains the drawbacks of this prior art process:

> "Final resolution and separation of LY146032 from structurally similar compounds is impeded by the presence of impurities which are not identifiable by ultraviolet analysis of the fermentation broth. These so-called "non-uv" impurities are primarily saponins and other fragments. These compounds have solubility characteristics similar to LY146032 and are difficult to separate from LY146032. The presence of these compounds causes foaming during concentration procedures and poor resolution during subsequent chromatographic separation steps.
>
> Attempts to remove these impurities by various chromatographic methods, including reverse-phase chromatography on silica gel/C18 (Quantum LP-1), normal phase chromatography over silica gel, and ion-exchange chromatography, failed to significantly improve the purity of LY146032 over the use of HP-20 as described above. All of these methods are plagued by low, capacity, poor resolution and low recovery of LY146032."

286. US 843 then describes its solution to these problems. It explains that the first HP-20 step of the prior art should be replaced with a "reverse method" procedure, wherein

adsorption is carried out with the non-functional resin in aqueous phase (polar) and resolution is carried out with the resin in organic phase (non-polar). It claims that since the "reverse method" removes the impurities that interfere with the subsequent purification steps, it improves the final purity from about 80% to about 93% and also improves the yield.

287. There are two issues concerning the disclosure of US 843, which were the subject of some debate between the experts. First, the meaning of "partially purified process streams", and secondly, what the document discloses about ion exchange chromatography.

288. In my judgment, the reference in US 843 to "partially purified process streams" would be understood by the skilled team to mean a solution of daptomycin that had already been concentrated by solvent removal prior to any of the HIC steps referred to in 843; Myerson T6/680/24-681/23. Accordingly, contrary to Cubist's submissions, US 843 is not a complete description of every step of a purification process for producing daptomycin.

289. Cubist submits that US 843 teaches that ion-exchange chromatography did not improve the purity of daptomycin. I do not agree. The passage which I have quoted states that "Attempts to remove *these impurities* by various chromatographic methods including… ion-exchange chromatography, failed to significantly improve the purity of [daptomycin] over the use of HP-20 as described above." "These impurities" is a reference to the non-UV impurities that are referred to in the preceding paragraph. I accept Dr Baker's evidence that this does not indicate that AEC was entirely unsuitable for the purification of daptomycin, but merely that it did not remove the non-UV impurities. The disclosure of US 843 is that use of the reverse method has succeeded in removing the non-UV impurities. Therefore, the skilled person would understand that this enables other chromatographic steps to be carried out, given that the non-UV impurity problem has been solved.

Obviousness over US 843

290. Cubist claims that Hospira's case of obviousness over US 843 is a classic hindsight, step-by-step analysis. In particular, it relies on the following submissions.

    i) That US 843 is a complete process for producing daptomycin. If the skilled person wish to purify daptomycin further, then the obvious approach in the light of US 843 would be to perform further HP-20ss purifications.

    ii) That Dr Baker's approach of considering sequential chromatographic steps of AEC, HIC and AEC ignored the other purification techniques that would have been known and available to the skilled person and was indicative of hindsight.

    iii) That AEC would not have been an obvious choice for a purification technique in the light of US 843, which only discusses hydrophobic interaction chromatography.

iv) That since US 843 teaches that ion-exchange chromatography did not improve the purity of daptomycin, the skilled person would consider that ion-exchange chromatography was not useful for the purification of daptomycin.

v) That a skilled person who reviewed the lipopeptide literature would have seen that the usual way that lipopeptides were purified was by the Cooper method i.e. precipitation by HCl, DCM extraction and recrystallisation, and not ion-exchange chromatography.

vi) That Dr Baker gave no reason for suggesting the choice of AEC as a first step, other than that it was a known and available technique commonly used for proteins. The skilled team would not consider that just because a technique worked for proteins it would also work for lipopeptides.

vii) That the skilled reader, seeing that Lilly had not adopted AEC in US 843, would have assumed that this was because ion-exchange chromatography had not improved the purity of daptomycin.

viii) Alternatively, that even if the skilled person would have included AEC on a list of possible techniques to try, he would not have any expectation of success.

ix) That US 843 warned against having too many purification step, and Dr Baker's approach of adding further steps went against this teaching

x) That adding an AEC step onto the end of the US 843 process was merely one of a number of choices. Merely being one option in a research project does not make a technique an obvious choice.

xi) That it was not obvious to perform HIC as the second step after AEC, given that multiple purifications using the HP 20 SS column disclosed in US 843 would already have been performed.

xii) That it was not obvious to use AEC in the final step for the same reasons that it was not obvious to use AEC as the first step.

xiii) That both claim 1 and claim 3 required that a chaotropic agent should be used in the AEC buffer. There was nothing in US 843 about the use of chaotropic agents and nothing to suggest that one might be needed.

xiv) Even though chaotropic agents were a known technique for preventing aggregation, the skilled person would not have any particular expectation of aggregation with a lipopeptide.

xv) That, in the light of the Kirsch paper, the skilled person would believe that it was not possible to separate daptomycin from anhydro-daptomycin and the beta isomer because of re-formation of the equilibrium. Therefore, he would have no reasonable expectation that an AEC step with a modified buffer would succeed.

xvi) That the secondary evidence refuted the case of obviousness since (a) Lilly had told Cubist that ion-exchange chromatography would not work for

> daptomycin; (b) the Lilly scientists were convinced the daptomycin could not be separated from anydro-daptomycin and the β isomer because of the existence of the equilibrium between those two molecules; (c) in relation to chaotropic agents this solution had not been obvious to Mr Downey of Cubist and was only identified by Mr Lynch and (d) if it was obvious to do an AEC step, there was no answer the question as to why Lilly did not do it.

291. Attractively as these submissions were put by Mr Hinchliffe, I do not accept them. They depend, crucially, upon a series of propositions which I have already rejected: in particular, that US 843 disclosed a complete process for the purification of daptomycin; that US 843 taught that ion-exchange chromatography did not improve the purity of daptomycin; that aspects of the common general knowledge would have put the skilled person off AEC for lipopeptides; that the skilled person would have wrongly believed that the equilibrium issue meant that daptomycin could not be purified to a greater extent than disclosed in 843; and that the secondary evidence is sufficiently complete to enable me to conclude that it was representative of what the skilled person would have done in the light of the disclosure of 843.

292. In my judgment, all the claims of the 179 Patent, said to be independently valid, are obvious. I reach this conclusion for the following reasons:

Motivation to improve US 843

293. There was an obvious motivation for the skilled team, when reading US 843, to improve the purity of daptomycin to a higher level than 93%. This is obvious for a pharmaceutical that is to be administered to humans, as Dr Baker made clear and Prof Myerson accepted.

Use of AEC

294. The skilled person reading US 843 in the light of common general knowledge about the use of different modes of purification to target different properties of the molecule would be surprised by the use of multiple HIC steps in US 843. Both experts were agreed that an obvious improvement to US 843 would be to use multiple modes of purification, of which one routine option was ion-exchange chromatography. Dr Baker resisted the suggestion that this was hindsight on his part, and I found his evidence convincing; he said at T4/406/18-407/2:

> "No, I do not think hindsight has anything to do with it. If you had asked me in 2000, when I was much more closely being at the bench, or pre-2000 at the bench doing chromatography and you had asked me the same question or the same sorts of questions, is doing hydrophobic interaction chromatography again and again and again a good idea, I would have said no. I would have said that it would be better to include a different sort of chromatography, and ion-exchange chromatography to try and effect a better purification."

295. Prof Myerson gave similar evidence, on the basis that the skilled team was starting with the process of US 843 and was seeking to improve it, which I have found there was an obvious motivation to do. He said at T6/680/12-20:

> "A. I see. If they were starting with this process I would agree you would look for another method of separation to improve the purity rather than continuing with HIC. I would agree with that.
>
> Q. One routine choice would be ion-exchange chromatography?
>
> A. It would be one of a number of potential choices of chromatographic and non-chromatographic separation techniques."
>
> Q. A routine one?
>
> A. It is on the list of things that you would look at."

AEC as the first step

296. Since US 843 expressly refers to starting its purification process with partially purified daptomycin, a standard way to achieve that partial purification was to use AEC as a first step, because it was well known simultaneously to reduce the volume of the solvent and to purify the substance. Since I have found that US 843 does not contain a general teaching that AEC will not work for daptomycin, there was nothing to deter the skilled team from using this standard method on the fermentation broth.

HIC followed by AEC

297. US 843 already discloses the use of the reverse HIC method. After HIC the skilled person would need to carry out a step to remove the solvent. I have found that AEC was well known as a standard way to remove the solvent and to obtain improved purity. Since US 843 teaches that its reverse HIC method removes non-UV impurities, there was no reason for the skilled team to believe that such non-UV impurities would impede use of AEC after HIC.

Use of buffers and chaotropic agents

298. I have found that using buffers, including Tris, was standard practice. I have also found that urea was a standard addition to an AEC column in order to avoid or remove aggregation. I do not accept Cubist's case that the skilled person would have no expectation of aggregation in lipopeptides and that finding this out would amount to a research project. The results of the AEC process would produce broad peaks, as Dr Kelleher explained were found by Mr Lynch. Aggregation would be on the standard list of possible reasons for such broad peaks and urea would have been a standard troubleshooting step to address this problem. This was the view of Dr Baker, which was accepted by Prof Myerson at T5/662/25-663/22.

Fair prospect of success

299. In my judgment the skilled team would consider that there was a fair prospect of success in improving the method of US 843. The steps which I have referred to above were routine, precisely because they were known at the priority date to be useful for improving purity. I do not consider that they are examples of the hindsight driven, step by step approach, which was deprecated by Lord Diplock in *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC 346 at 362. On

the contrary, I consider that they are a standard application of techniques known at the priority date to improve purity.

The secondary evidence

300. Mr Hinchliffe makes a powerful point that if it was obvious that the method of US 843 could have been improved by simple, standard steps, then Lilly would have done this. He also relies on the fact that when Cubist began its purification process of daptomycin, in collaboration with certain Lilly consultants, the process did not prove easy to develop, until Mr Lynch was consulted.

301. However, when considering whether this provides an answer to obviousness, I have borne in mind that relevant witnesses with personal knowledge of the development, both from Lilly and Perseptive, were not called by Cubist, and so it has not been possible to gain a real understanding of the decisions made and the reasons for making them. Furthermore, my assessment of the expert evidence of Dr Baker and Prof Myerson leads me to the conclusion that the 179 Patent is obvious in the light of US 843. I consider that Lilly held a particular view, which would not have been shared by the notional skilled team, that AEC was unsuitable for the purification of daptomycin and that, because of the equilibrium issue, daptomycin could not be separated from certain impurities.

302. Mr Lynch was given very little information about how to purify daptomycin and managed to do so in a few weeks. Cubist did not present a positive case that the approach that Mr Lynch took was in any way difficulty or unconventional. I consider that his approach is representative of the steps that would have been taken by the skilled team when seeking to improve US 843. I consider that the difficulties encountered by Cubist were as a result of views expressed to it by Lilly, which would not have been shared by, or known to, the notional skilled team.

Conclusion

303. For these reasons, I find that claims 1 and 3 of the 179 Patent are obvious in the light of US 843. I consider that claim 4 is also obvious. Claim 4 includes a particular feed level condition which the skilled person would routinely reach by adjusting fermentation feed conditions to encourage production of daptomycin. This was explained by Dr Baker at T4/443/23-444/18, and I accept his evidence. Given that I have found that claims 1 and 3 lack inventive step, it is conceded by Cubist that claim 5 is invalid. This concession was rightly made, because Prof Myerson explained during his cross-examination that claim 5 added nothing inventive over claims 1 and 3.

Obviousness of the 179 Patent over common general knowledge alone

304. Strictly, it is unnecessary for me to consider the remaining objections to validity of the 179 Patent, given my conclusion that it lacks inventive step over US 843. Nonetheless, in case I am wrong, I will decide the remaining invalidity objections, albeit fairly briefly.

305. A number of cases make clear that an argument that a patent is invalid over common general knowledge alone needs to be treated cautiously. This is because the

combination of features relied on is created with hindsight knowledge of the claims of the patent, and inventive combinations can often be made to appear obvious after the event. Floyd J dealt with this question in *Ratiopharm v Napp* [2008] EWHC 3070 (Pat); [2009] RPC 11 at [158]:

> "158. Fourthly, allegations of obviousness in the light of common general knowledge alone need to be treated with a certain amount of care. They can be favoured by parties attacking the patent because the starting point is not obviously encumbered with inconvenient details of the kind found in documentary disclosures, such as misleading directions or distracting context. It is vitally important to make sure that the whole picture presented by the common general knowledge is considered, and not a partial one."

306. Giving due weight to this, and other warnings in the case law, I have nonetheless reached the conclusion that claim 1 of the 179 Patent is obvious over the common general knowledge alone. The scope of claim 1 includes the use of Tris (a standard buffer) and urea (a standard agent for use in an AEC column in order to avoid or remove aggregation) in an AEC process (a standard purification process). Since I have found that there is nothing about lipopeptides, or daptomycin, to deter the skilled person from using AEC to purify daptomycin, this is a case where this claim is obvious in the light of common general knowledge.

307. On the other hand, I do not consider that claim 3 is obvious over common general knowledge alone. My reasons are as follows. First, and in contrast to the case of obviousness over US 843, there is no starting point which would lead the skilled person to the combination of claim 3, by routine improvements. Secondly, I am not satisfied that, without US 843, the skilled team would be able to solve the problem of removal of non-UV impurities (which US 843 has dealt with) by the application of common general knowledge alone. Thirdly, a part of this attack was based on the proposition that claim 3 was a mere collocation of known purification steps. Insofar as this suggests that the order of steps in claim 3 does not matter, I disagree. The order does matter, and affects purification. Fourthly, Hospira's attack based on common general knowledge relied upon the deposition of Mr Lynch's evidence, as set out in his deposition. In the absence of a Civil Evidence Act Notice, I have held that the only evidential value of this deposition is the answers that were given by Dr Kelleher when he was cross-examined about it.

308. In summary, the skilled person would read US 843 in the light of common general knowledge, and that, in my judgment, leads to a conclusion of obviousness. I would not reach the same conclusion about the combination claimed in claim 3 based on common general knowledge alone. Since claims 4 and 5 are dependent on claim 3, in my judgment, they are not obvious based on common general knowledge alone.

Added matter

Legal principles

309. Legal principles of relevance to the present case are as follows:

i) The test of added matter is whether a skilled person would, upon looking at the amended specification, learn anything about the invention which he could not learn from the unamended specification; *Vector Corp v Glatt Air Techniques Limited* [2007] EWCA Civ 805; [2008] RPC 10 at [4], approving Jacob J in *Richardson-Vicks Inc's Patent* [1995] RPC 568 at 576.

ii) One reason for the rule against adding matter is that third parties should be able to look at the application and draw a conclusion as to the subject matter which is available for supporting the claimed monopoly. If subject matter is added subsequently, the patentee could obtain a different monopoly to that which the application originally justified; *AP Racing Ltd v Alcon Components Ltd* [2104] EWCA Civ 40; [2014] RPC 27 at [9]-[10].

iii) The test of whether the skilled person is confronted with new information depends on whether the combination of claimed features in the patent derives directly and unambiguously from the application, read as a whole. It is not necessary for the subject-matter of the amendment to have been explicitly disclosed in the application. Literal support is not required by Article 123(2) (T 667/08 of 20 April 2012, and the EPO Guidelines for Examination Part H, Chapter IV, §2.2).

iv) An intermediate generalisation occurs when "a feature is taken from a specific embodiment, stripped of its context and then introduced into the claim in circumstances where it would not be apparent to the skilled person that it has any general applicability to the invention" (*Nokia v IPCom* [2012] EWCA Civ 805; [2013] RPC 5 at [56]).

v) The question is whether the feature in question would be seen by the skilled person as being generally applicable or only of significance in the context in which it was specifically disclosed. (*Nokia v IPCom* at [59]-[60].

vi) There is a distinction between what a claim covers and what it discloses. A claim may cover matter without disclosing it. The law does not prohibit the addition of claim features which state in more general terms that which is described in the specification. What the law prohibits is the disclosure of new information about the invention. *AP Racing* (supra) at [30]-[32].

The starting sample of daptomycin and obtaining "purified daptomycin" in combination with the purification steps of claim 1

310. Hospira alleges that whilst the application as filed teaches using daptomycin selected from the group described in claim 1, and separately teaches obtaining purified daptomycin in certain contexts, the application does not teach the skilled team that daptomycin selected from the relevant group would be purified daptomycin using steps (b)-(d) in claim 1. This objection arises from the addition of the words in feature (e) of claim 1 "obtaining purified daptomycin".

311. In the patent as granted, "purified daptomycin" includes daptomycin that is at least 95% pure, and also includes daptomycin that has reduced levels of other impurities (see [0034]).

312. It is clear from the application as filed that there is a general teaching that its invention is directed at obtaining purified daptomycin. For example, the summary of the invention at p. 6 lines 5-9 of the application states that:

> "In one embodiment of the instant invention, commercially feasible methods are disclosed that result in daptomycin at a purity level of 95 to 97%. In another embodiment of the instant invention, a commercially feasible method is disclosed that almost completely eliminates the major impurities anhydro- daptomycin and β isomer as well as other impurities in preparations of daptomycin."

So the application is directed at obtaining "purified daptomycin" as that term is used in claim 1 of the granted patent.

313. The use of modified buffer enhanced ion-exchange chromatography to produce purified daptomycin is disclosed at p.22 lines 13-21 of the application:

> "Another embodiment of the instant invention is drawn to a chromatography method that produces a highly purified lipopeptide not achievable by prior art chromatography methods. The chromatography method comprises the use of modified buffer enhanced anion exchange chromatography to purify a preparation containing a lipopeptide. In a preferred embodiment, the method is used to produce highly purified daptomycin or a daptomycin related lipopeptide. This method, when used with partially purified daptomycin, produces daptomycin that is at least 98% pure. The method also produces daptomycin that is free or essentially free of anhydro-daptomycin."

314. Contrary to Hospira's submissions, this disclosure is not limited to use of the modified buffer AEC method with partially purified daptomycin as the starting material. That is simply one option.

315. Claim 11 of the application has the same steps (a) to (d) that appear in claim 1 of the 179 Patent as granted. There are two differences between claim 11 of the application and claim 1 of the 179 Patent. First, claim 11 lists out the classes of purified daptomycin obtained by the process (for example, essentially pure, or 98% pure, daptomycin). Secondly, claim 11 does not contain step (e) of claim 1 as granted, "obtaining purified daptomycin".

316. However, in my view, neither of these differences add matter, particularly when claim 11 is read in the light of the whole disclosure of the application. In relation to the classes of daptomycin set out in the opening words of claim 11, these are all within the definition of "purified daptomycin" in the 179 Patent as granted. In relation to step (e) of claim 1, the whole point of the process disclosed in the application is to obtain purified daptomycin. While these exact words are not used in the opening part of claim 11, this preamble sets out the results of applying steps (a) to (d), which is to obtain purified daptomycin.

317. Accordingly, I reject this added matter attack, as I am satisfied that a skilled person would not, upon looking at the 179 Patent as granted, learn anything about the invention which he could not learn from the application. The objection is based on

form and not substance, and fails to have regard to the technical disclosure of the application when read as a whole.

318. Furthermore, if I had considered that the added matter objection would otherwise have been successful, I would have allowed Cubist to make its conditional amendment to include the definitions of the class of levels of purity of daptomycin to be produced by the process, which appear in claim 11 of the application, in claims 1 and 3 of the 179 Patent. The only remaining point would then be whether the addition of integer (e) "obtaining purified daptomycin" adds subject matter. It does not, because this step merely refers to obtaining the products identified in the preamble to the claim, as a result of process steps (a)-(d).

Claim 1 – list of chaotropic agents

319. This objection arises because the list of chaotropic agents in claim 1 is slightly shorter than that which appears in the application. In particular, in the application, the modified buffer is described as follows:

> i) a buffering agent, such as, without limitation, acetate, phosphate, citrate and Tris-HCl, or any other buffering agent that buffers well at neutral pH.
>
> (ii) one or more chaotropic agents, including, without limitation, guanidine, ammonia, urea, a strong reducing agent, benzoate, ascorbate or another ionic enhancer capable of modifying the buffer so that daptomycin is easily separated from impurities.

320. Although the whole of this passage appears in the specifications of both the application and the 179 Patent, the underlined language does not appear in claim 1 of the 179 Patent.

321. I do not consider that this adds matter. The claim has been limited to the specific examples given in the specification (with the exception of guanidine, which has not been claimed). The disclosure in the specifications of both the application and the 179 Patent is the same. This is a classic narrowing of the claim by amendment, which does not contain any new teaching.

Claim 3 – "purified daptomycin"

322. A similar added matter objection is advanced in relation to claim 3 as I have dealt with in relation to claim 1. Claim 3 of the 179 Patent is to a method of purifying daptomycin using a combination of AEC, HIC and modified buffer AEC. Claim 15 of the application contains the same chromatography steps as claim 3 of the 179 Patent but differs in that it has a list of the class of purified daptomycins to be produced in its preamble and also does not end with the conclusory words "to obtain purified daptomycin".

323. I reject this added matter objection for essentially the same reasons as I rejected it in respect of claim 1. In particular, the application discloses in general terms the purification of daptomycin using the three step process as is claimed in claim 3. A preferred embodiment of this method is disclosed to produce daptomycin that is 98%

pure or is substantially or essentially free of anhydro-daptomycin or the β isomer. This is "purified daptomycin" as defined by para [0035] of the 179 Patent.

324. Furthermore, there are no differences of substance between claim 3 of the 179 Patent and claim 15 of the application. Finally, if I had thought that there was added matter, I would have allowed Cubist to make the conditional amendment to claim 3 to introduce the classes of daptomycins produced by the process of the claim into the preamble of claim 3.

Enablement across the full width of the claims

325. This ground of invalidity was relied on as a squeeze with the prior art, in that it was alleged that the claims of the 179 Patent were not enabled insofar as they cover methods which do not use the method described in US 843. This was not referred to in Hospira's closing speech. Given that I have decided that the 179 Patent is obvious in the light if US 843 I do not believe that a squeeze with insufficiency arises.

The 047 Patent

The skilled team

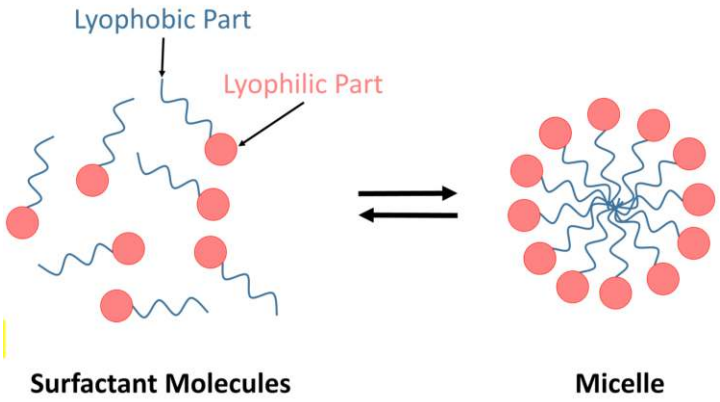
326. In general terms, the claims of the 047 Patent concern a method of purifying daptomycin through the formation and disassociation of aggregates of daptomycin molecules known as micelles. Neither party contends that the skilled team is any different for the 047 Patent than for the 179 Patent. Accordingly, my conclusions about the attributes and composition of the skilled team are the same for both Purity Patents.

Additional common general knowledge of relevance to the 047 Patent

Surfactants

327. The following was common general knowledge at the priority date. A surfactant is a substance that tends to lower the surface tension between two liquids or between a liquid and solid. Surfactants have a characteristic molecular structure in which part of the molecule has a strong attraction to the solvent (lyophilic) while another part has little attraction to it (lyophobic). A biological molecule that is a surfactant is referred to as a "biosurfactant".

328. Surfactants can aggregate under certain conditions to form micelles. A micelle is a number of surfactant molecules arranged together with the lyophilic parts of the molecule facing out and the lyophobic parts facing in, as shown in a diagram from Prof Myerson's first report.



Such micelles form as the concentration reaches the "critical micelle concentration" ("CMC").

Lipopeptides as surfactants

329. There was some dispute as to whether it was common general knowledge that lipopeptides, as a class, were treated as biosurfactants. Prof Myerson had not worked with lipopeptides and so he did not know what those skilled in the field thought the time. However, it was his opinion that there might be extreme cases where a lipopeptide might not behave as a surfactant, for example if it was insoluble.

330. In my judgment, it was widely known that lipopeptides, as a class, were biosurfactants. I accept the view of Dr Baker on this issue, which was amply demonstrated by literature published before the priority date. For example, Desai and Banat (1997) (supra) stated that a "large number of cyclic lipopeptides… possess remarkable surface-active properties." Lin et al. (1994) (supra) stated that "among the many classes of biosurfactants, lipopeptides are particularly interesting because of their high surface activities and therapeutic potential". There were no examples in evidence of a lipopeptide which had been shown not to act as a surfactant.

Primary structure of lipopeptides

331. There was no dispute that in order to be a surfactant, a molecule must have hydrophobic and hydrophilic portions, and that cyclic lipopeptides possess this structure. Dr Baker explained that at the priority date, the primary structure of a lipopeptide was considered sufficient for the purpose of making a reasonable prediction that it would act as a surfactant. That may have been somewhat simplistic, but that was how categorisation was performed at the priority date. I accept his evidence. The literature before the priority date showed that those in the field who considered lipopeptides expected that they would behave as surfactants based on their primary structure.

332. Cubist submits that this is too simplistic an analysis and that if the three-dimensional structure of a lipopeptide was considered, then far more information about the molecule in question would be revealed, from which it might be concluded that it was not a surfactant. However, I do not consider that those in the field of lipopeptides at the priority date were concerned with their three-dimensional structure. Rather, they were able to make reasonable predictions about surfactant behaviour of a lipopeptide based on primary structure. Dr Baker explained, and I accept, that there was no need

to know the three-dimensional structure of a lipopeptide in order to test its surfactant properties.

Daptomycin as a surfactant

333. Cubist points out that although there was literature on daptomycin by 2000, none of it reported that daptomycin was a surfactant. This is correct. However, daptomycin was known to be a lipopeptide. Furthermore, it has a primary structure which Dr Baker characterised as a "tennis bat model". It has a hydrophilic head and a hydrophobic tail, and its primary structure was even more suggestive of a surfactant than the well-known biosurfactant "surfactin". Dr Baker explained this during cross-examination at T4/478/11-24:

> "A. I think the very simple model, which I will call the tennis bat model, with the ring being, or the head of the tennis bat being, the hydrophilic parts and the handle being the hydrophobic parts -- is the diagram that appears in the specification as well about how micelles are formed. That at the time was the generally accepted way of how surfactin was arranged. All the diagrams show the hydrophobic tail pointing down and the hydrophilic head pointing up. I agree that when you look at the actual arrangement of the amino acids, it is perhaps counterintuitive. However, we know that it is a biosurfactant. If you look at the daptomycin, there is actually a bit of a clearer distinction between the hydrophilic head and the hydrophobic tail -- just by looking at the primary sequence…."

334. I accept that the skilled team would not be certain that daptomycin was a biosurfactant without testing whether this was the case. However, given that the molecule was a lipopeptide, which was known as a class to be biosurfactants, and given that its primary structure strongly suggested that it was a surfactant, the skilled team would have a strong expectation that this would be the case.

Tests to determine whether a lipopeptide is a surfactant

335. There were a number of standard tests at the priority date which were easy to perform, to check whether a molecule was a surfactant. First, there was the "shake test". Dr Baker explained that a surfactant will produce a stable foam on shaking, whereas a non-surfactant will either not form a foam, or will form a transient foam that quickly disappears. Additionally, a surfactant produced by fermentation might be expected to form a stable long-lasting foam during the fermentation process.

336. This gave rise to some evidence from Dr Kelleher, which was relied on by Cubist to suggest that the skilled team would not conclude that daptomycin was a surfactant. In particular, Dr Kelleher said that he had not seen foam when working on daptomycin in the fermentation broth, and that he had shaken test tubes of daptomycin to make the mixture homogeneous, and had not seen a stable foam. Whilst I have no reason to doubt what Dr Kelleher said, I do not consider that this evidence suggests that, contrary to the fact, daptomycin would be considered not to be a surfactant.

337. In particular, Cubist used a de-foaming agent in its fermentation broth, deliberately to avoid foaming, and therefore it is unsurprising that Dr Kelleher had not observed this

phenomenon. Furthermore, for understandable reasons, Dr Kelleher was unable to give specifics of the containers which he shook. Finally, the purpose of Dr Kelleher's shaking was to make the mixture homogenous, and in those circumstances it was important to avoid excessive shaking. Such considerations would not apply to the "shake test", the object of which is to see whether a strong stable foam can be created.

338. In any event, Prof Myerson explained that various tests which measure the surface tension of the fluid could be carried out using very simple equipment. Prof Myerson's preferred approach was to measure the CMC by electrical conductivity, which at the same time established whether or not the molecule was a surfactant. These tests were common general knowledge at the priority date and could be performed simply in any reasonably equipped laboratory.

339. I find, on the balance of probabilities, that any of these tests would have confirmed the expectation of the skilled team that daptomycin was a biosurfactant.

Common general knowledge of surfactin at the priority date

340. Cubist accepts that surfactin is a lipopeptide and a biosurfactant, and that many published papers on lipopeptides at the priority date concerned surfactin. However, Cubist submits that the skilled person would not necessarily have heard of surfactin as a matter of common general knowledge. Given that the skilled team would have conducted a literature search on lipopeptides before attempting to purify daptomycin, I find that it would quickly learn of surfactin, if it did not know about it already.

341. The evidence established that surfactin was well known as the model biosurfactant. Dr Baker described it as the most well characterised biosurfactant at the priority date and Prof Myerson described it as "the poster child" of biosurfactants. Cubist submits that because surfactin was an unusually strong surfactant it readily formed micelles. This would not lead the skilled team to appreciate that daptomycin was likely to be a biosurfactant. I reject this. I have already dealt with the strong expectation of the skilled team that daptomycin was likely to be a biosurfactant. Furthermore, given that surfactin was the model biosurfactant, it was conventional for those working on potential biosurfactants at the priority date to follow the surfactin literature. Dr Baker explained that when he was working on lipopeptides of unknown origin from fermentation, he used purification methods for surfactin, because it was the model lipopeptide.

Formation of micelles

342. Cubist submits that the CMC is dependent on the structure of a molecule and the conditions. If a solution contains additional dissolved species these could affect the ability of a given compound to form micelles. I accept that skilled team would know that the formation of micelles was dependent on a number of factors, but it would also be aware, as a matter of common general knowledge, of which factors affected the CMC and therefore influenced micelle formation. In particular, manipulating temperature, the addition of solvent and the addition of electrolyte, were well known methods of influencing micelle formation.

343. There was a dispute as to whether manipulating the pH was also a well known way of influencing micelle formation. Cubist's case is that changing the pH was not

recognised at the priority date as a way of controllably forming and breaking micelles. pH was not referred to in this context in the literature published before the priority date. However, Dr Baker's view was that varying the pH was well known to vary the propensity for a lipopeptide biosurfactant to exhibit surfactant properties, including the formation of micelles. Adjusting the pH with the addition of an acid or an alkali could be controlled very closely, and the CMC could be varied; Baker 1 [4.45] and [8.27].

344. During his cross-examination, Prof Myerson gave similar evidence, for similar reasons. He was cross-examined on this issue at T6/698/11 -702/23, and was asked about the disclosure in the 047 Patent of ways of controlling the CMC:

> "There is nothing particularly special, is there, professor, about using the pH to control the CMC? It is just one of a number of different ways you could control the CMC if you wanted to control the CMC?
>
> Right, but the nice thing about the pH swing is that you do minimal alteration to the solution to form and disassociate the micelles. In a separation process the ideal thing is not to add much, if anything, to the solution that you're going to have to get out again so pH swing is a good method from that basis."

345. In order to investigate how changes in pH or temperature would affect the stability of the solution and the CMC, it was common general knowledge to perform a routine CMC study. One such CMC study which investigates changes in pH on surfactin is shown in Figure 1 of the Cooper paper (supra).

The specification of the 047 Patent

346. I will refer to passages in the specification which are relevant to micelle formation, which I have not discussed in the context of the 179 Patent. [0001] states (amongst other things) that:

> "The present invention relates to a process for preparing the highly purified form of the lipopeptide daptomycin. The present disclosure further relates to micelles of lipopeptides. The present disclosure also relates to pharmaceutical compositions of the lipopeptide micelles and methods of using these compositions. The present invention also relates to methods of making daptomycin micelles from non-associated monomers of daptomycin, and for converting daptomycin micelles to non-associated monomers. The present invention also relates to a process for preparing daptomycin using micelles that is easily scaled for commercial production."

347. So the specification proceeds on the basis that lipopeptides will generally form micelles, and that its methods are applicable to lipopeptides in general and daptomycin in particular. Similarly, the various definitions of "micelle", "mixed micelle", etc. at [0040]-[0043] refer to lipopeptides generally, rather than being confined to daptomycin. Daptomycin is treated as an example of a lipopeptide, rather than as a special case.

348. The section beginning at [0081] onwards is entitled "Formation of Lipopeptide Micelles and Methods of Use Thereof". [0084]-[0092] disclose a number of different ways in which the CMC for a lipopeptide can be manipulated in order to form or dissociate micelles. In particular:

    i) [0085] states that "in one embodiment of the disclosure, the CMC of a lipopeptide may be manipulated by adding or subtracting a CH2 group to the lipopeptide;"

    ii) [0087] states that "in one embodiment of the invention, the CMC of a lipopeptide is manipulated by changing the temperature of the solution comprising the lipopeptide";

    iii) [0089] states that "in a further embodiment of the invention, the addition of an electrolyte is used to decrease the CMC of an ionic lipopeptide";

    iv) [0092] states that "in the invention, the pH of a solution comprising daptomycin is manipulated to influence the CMC of the daptomycin. The pH is manipulated so that the concentration of a lipopeptide is higher than the CMC at one pH and is lower than the CMC at another pH ".

349. In summary, the 047 Patent specification lists the methods for varying the CMC, and therefore manipulating the formation of micelles, which I have found to be common general knowledge at the priority date. [0092] gives a little more detail in respect of daptomycin. It discloses that at lower pH (pH 4.0) the CMC of daptomycin is lower than at pH 6 or 7.5. Thus, daptomycin can be encouraged to form micelles by lowering the pH. But again, daptomycin is not presented as a special case, with a particular problem to solve, in contrast to other lipopeptides.

350. Paragraphs [0095]-[0102] set out the purification method that is reflected in the claims of the 047 Patent. The daptomycin is first formed into micelles by lowering the pH. The solution is then passed through an ultrafiltration membrane. The daptomycin micelles are retained on the filter, but smaller impurities pass through. Then the daptomycin that was retained on the membrane has its pH adjusted upwards to pH 6.5, causing the daptomycin micelles to break apart. The solution is passed through another ultrafiltration step. This time, the daptomycin monomers are able to pass through the filter, but larger impurities are retained on the filter, thereby separating them from the daptomycin.

Claim 1 of the 047 Patent

351. Only claim 1 is sought to be defended as independently valid. It claims:

> "1. A method for purifying daptomycin comprising:
>
> (a) subjecting the daptomycin to conditions in which a daptomycin micellar solution is formed by altering the pH;
>
> (b) separating the daptomycin micelles in the daptomycin micellar solution from low molecular weight contaminants by a size separation technique;

> (c) subjecting the daptomycin to conditions in which a daptomycin monomeric solution is formed by altering the pH; and
>
> (d) separating the monomeric daptomycin molecules in the daptomycin monomeric solution from high molecular weight molecules or aggregates by a size separation technique."

352. As with the 179 Patent, claim 1 the 047 Patent is not limited to the purification of daptomycin on a commercial scale, and includes purification on a laboratory or pilot scale.

The disclosure of Lin & Jiang

353. In the introduction to Lin & Jiang, the authors note that the approaches to purification of biosurfactants that existed at the time had drawbacks. They observe that at concentrations above the CMC, surfactant molecules associate to form supramolecular structures, such as micelles or vesicles, with nominal molecular diameters up to two to three orders of magnitude larger than that of the single un-associated molecules. They acknowledge that these properties had already been exploited to recover surfactin from a complex fermentation medium as described by in a paper by Mulligan & Gibbs, published in 1990.

354. Lin & Jiang describe a process for purifying surfactin that seeks to improve the Mulligan & Gibbs process. First, they formed micelles and removed certain low molecular weight impurities via ultrafiltration. Lin & Jiang then removed high molecular weight impurities that were retained on the ultrafiltration membrane together with the surfactin micelles by adding methanol to the ultrafiltration membrane to break the micelles into monomers, such that the monomeric surfactin passed through the filter, while the high molecular weight impurities were retained on the filter.

355. Lin & Jiang concluded:

> "This process can be further modified and employed for the recovery and purification of most surfactants from aqueous solutions at concentrations above the critical micelle concentration."

Obviousness of the 047 Patent in the light of Lin & Jiang

356. The differences between claim 1 of the 047 Patent and Lin & Jiang are as follows: first, Lin & Jiang concerns the purification of surfactin, rather than daptomycin and secondly, Lin & Jiang uses methanol to dissociate the micelles in its second step, rather than manipulating the CMC by altering the pH.

Purification of surfactin and daptomycin

357. Cubist submits that it would not be obvious to apply the teaching of Lin & Jiang to daptomycin, because daptomycin would not form part of the common general knowledge of the skilled addressee of the Purity Patents and a clinician would not be a part of the skilled team. I have already rejected this submission in relation to the 179 Patent. I reject it for the same reasons in relation to the 047 Patent.

358. Alternatively, Cubist submits that even if the skilled person reading Lin & Jiang was aware of daptomycin, it would not be obvious, with the relevant fair expectation of success, that the approach in Lin & Jiang could be applied successfully to the purification of daptomycin. In particular, Cubist contends that:

    i) the Lin & Jiang method would not be expected effectively to remove pyrogens;

    ii) the skilled team would not consider that daptomycin was likely to be a surfactant which would form micelles;

    iii) it was not obvious to form and disassociate the micelles disclosed in Lin & Jiang by changing pH, rather than by using methanol.

359. As to the first issue, Cubist draws attention to the cross-examination of Dr Baker at T/4/453- 461. In particular, it relies on the fact that Dr Baker did not consider that the Lin & Jiang method alone would remove all pyrogens; see, for example, T/4/456/24-457/8:

> "A. Yes. I mean, what you are suggesting is that it is almost as though you are going to use this method alone for the purification of surfactin or daptomycin and I think in both cases, I know surfactin is not an injectable, but I think this method alone is not sufficiently safe to guarantee the removal of pyrogens in either case, just because the formation of micelles can always carry along – you would need another one of the normal methods for reducing pyrogens to ensure that there was no pyrogen contamination."

360. Prof Myerson agreed that the skilled reader of Lin & Jiang would not assume that its method could remove all impurities and that he would expect it to be used together with other purification steps. He considered that the same was true in respect of the purification method of the 047 Patent; T5/549/11-550/4. In my judgment, he was right about this. There is nothing in the 047 Patent which requires micelle formation and disassociation to remove all impurities. On the contrary, example 15 at [0183] applies repeated chromatography steps, in addition to the method claimed in the 047 Patent, to purify daptomycin. As a result, it is stated that "pyrogen content is reduced to undetectable levels."

361. Accordingly, I do not consider that the skilled team would regard the micelle formation and dissociation processes of Lin & Jiang and the 047 Patent as total purification methods. It would appreciate that pyrogens may remain, and in both cases could be removed by standard steps. I do not consider that the skilled team would reject either of these methods because of the further requirement to remove pyrogens.

362. In addition, claim 1 of the 047 Patent does not require that all pyrogens should be removed as a result of application of its method to daptomycin. Indeed, it does not contain any requirement for a minimum purity level for daptomycin, following application of the claimed method. Therefore, this does not distinguish the claimed invention of the 047 Patent from Lin & Jiang.

363. Finally, I have rejected Cubist's contention that the skilled team would not consider that daptomycin (in contrast to surfactin) was likely to be a surfactant which would form micelles. My conclusion is that the skilled team would have a real expectation that daptomycin was a surfactant likely to form micelles, and would be able to confirm this by straightforward, routine testing.

Manipulating the CMC by altering the pH

364. I consider that the skilled team reading Lin & Jiang would very quickly appreciate that the use of methanol in the purification of a pharmaceutical to be administered to humans was undesirable, and would look for another way to dissociate the micelles. Controlling the pH was one of three standard ways of doing this, along with temperature control and the addition of electrolyte. I set out my reasons for this conclusion in more detail below.

Assessment of obviousness in the light of Lin & Jiang

365. I have concluded that the 047 Patent is obvious in the light of Lin & Jiang. My reasons are as follows.

366. First, although Lin & Jiang concerns the purification of surfactin, the skilled team would appreciate that it proposes a method for use with biosurfactants generally. Indeed, it expressly states that its method can be further modified and employed for the recovery and purification of most surfactants from aqueous solutions at concentrations above the critical micelle concentration.

367. Secondly, the skilled team would appreciate that the method taught by Lin & Jiang was of potential relevance to the purification of daptomycin. It would have a real expectation that daptomycin was a biosurfactant which would form micelles, based on its primary structure, and the fact that it was a cyclic lipopeptide, which it could confirm by simple tests.

368. Thirdly, the skilled team would regard Lin & Jiang as disclosing a workable method to purify biosurfactants on a laboratory scale and would regard the first step of forming micelles and using ultrafiltration to remove the smaller impurities as useful. However, the experts agreed that it would immediately be appreciated that methanol should not be used in the second step to manipulate the CMC to disassociate the micelles, for anything other than proof of concept, which was the object of the Lin & Jiang paper. Prof Myerson explained that the first disadvantage of using methanol was that it is toxic so it would have to be removed to a very low level. The second disadvantage was that Lin & Jiang used a lot of methanol, which would lead to problems of solvent recovery at the end of the process; T6/689/14-690/5.

369. Once the skilled team had decided to use an alternative way to manipulate the CMC to dissociate the micelles, in my judgment the evidence was clear that control of pH was one of a list of three standard ways of doing this. I have already referred, when considering common general knowledge to Dr Baker's evidence that changing the pH and changing the temperature would have been understood to be particularly good ways of manipulating the CMC because they were readily controllable; and to Prof Myerson's evidence that both of those methods were advantageous because they require fewer additions to the liquid solution. When considering Lin & Jiang Prof

Myerson accepted that pH control was one of three routine methods that would be considered to disaggregate the micelles.

> "Q. But as you say, somebody who was thinking of actually using it would very, very quickly see that the use of methanol was undesirable?
>
> A. I would hope so.
>
> Q. And it would be obvious to try and fix that?
>
> A. If you wanted to adopt this process you would look for another way to change -- to dissociate the micelles, I would agree with that.
>
> Q. You say to dissociate the micelles. Put it another way, to control the CMC?
>
> A. Yes.
>
> Q. And one that would be on a short routine list, and I suggest to you at the top of the list would be controlling the pH for all the reasons we have discussed.
>
> A. I think the reason we are all saying that is because we know it works. I do not know that I would walk in and say, hey, let us do this and let us control the pH to change the micellar composition of the solution or the CMC. If I was interested in reproducing this process, I would look at all the variables, I think that is fair, pH, temperature and the addition of electrolyte."

370. Finally, I have considered the secondary evidence of Dr Kelleher that Lilly did not tell Cubist that daptomycin behaved as a surfactant or formed micelles, and that Cubist apparently stumbled across the ability of daptomycin to for micelles when it clogged a 10,000 dalton MWCO filter. However, during cross-examination, Dr Kelleher explained that he had asked for daptomycin to be tested for micelle formation because "we knew it had a hydrophobic structure on it"; T3/279/22-280/2. This reflects the common general knowledge of cyclic lipopeptides as having a hydrophobic ring and hydrophilic tail, and therefore, likely to be biosurfactants. In any event, Dr Kelleher was unaware of Lin & Jiang when he developed the process of the 047 Patent, and his evidence does not provide an answer to obviousness over that prior art.

371. For these reasons, I conclude that the 047 Patent is obvious in the light of Lin & Jiang.

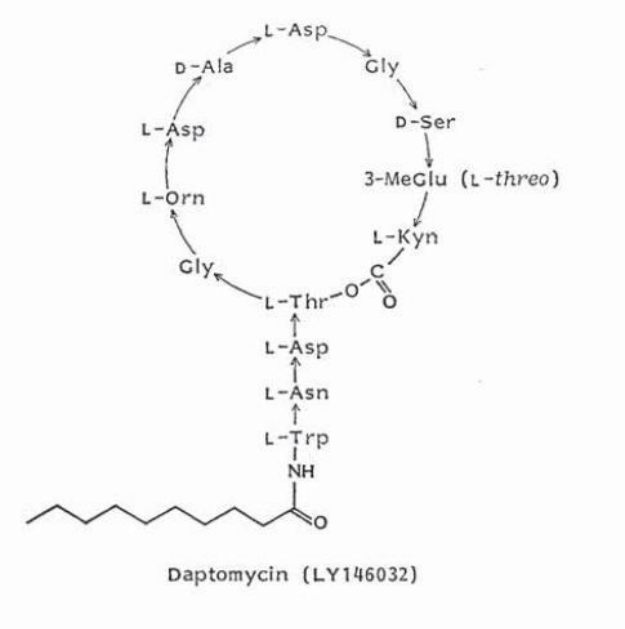
Daptomycin insufficiency

372. This validity attack is alleged to apply to all of the Patents. Hospira claims that each of the Patents describes daptomycin in such a way that it would be impossible for the skilled team to put the alleged invention into effect.

373. The argument can be illustrated by reference to [0003] of the 417 Patent. This states:

> **[0003]** Daptomycin is described in Baltz in Biotechnology of Antibiotics, 2nd Ed., ed. by W.R. Strohl (New York: Marcel Dekker, Inc.], 1997. pp. 475-435, hereafter "Baltz." Daptomycin is a cyclic lipopeptide antibiotic that can be derived from the fermentation of Streptomyces roseosporus. It is comprised of a decancyl side chain linked to the N-terminal tryptophan of a cycle 13-amino acid peptide (seen Fig 1a, Baltz et al., *supra*). The compound is currently being developed in both intravenous and oral formulations to treat serious infections caused by bacteria, including, but not limited to, methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci (VRE).

374. Figure 1a of Baltz, referred to in [0003] of the 417 Patent, shows a compound with the following stereochemistry:



Daptomycin (LY146032)

375. The important part of this figure for the purposes of the insufficiency attack is the "L-Asn" shown on the fatty acid tail portion. The "L" indicates that the asparagine amino acid has been given an absolute stereochemical assignment as a "right-handed protein".

376. Hospira submits that the skilled team reading the Patents would understand that the term "daptomycin" referred to the n-decanoyl derivative of the factor A21978C antibiotic produced by fermentation of Streptomyces roseosporus and which had the specific stereochemistry shown at Figure 1a of Baltz. However, it was and is impossible to make something which fulfils these criteria, because the product of the fermentation process described in the Patents has been shown by Miao et al (2005) not to have the stereochemistry shown in Baltz. Miao shows that the compound produced by way of the fermentation process is a compound with a "D" (or left-handed) asparagine amino acid ("D-Asn") in the fatty acid fail portion, instead of an L-Asn. It was common ground between the stereochemistry experts that Miao is right and Baltz is wrong.

377. Accordingly, Hospira alleges that the Patents are insufficient because they teach the skilled team to make something (i.e. something made from fermentation with the structure of figure 1A of Baltz) which cannot be made, and so the Patents cannot be implemented.

378. I do not accept Hospira's case on this issue, for the following reasons. First, this raises an issue of construction as to what the skilled team would understand "daptomycin" to mean in the context of the Patents. In my judgment, the Patents are not using "daptomycin" to refer to an antibiotic with the exact stereochemical configuration shown in Fig. 1A of Baltz. Rather, they are using the word in a practical sense, simply to refer to the product obtained from the fermentation of Strepomyces roseosporus.

379. In particular, the Patents specifically state that daptomycin can be derived from the fermentation of Strepomyces roseosporus; e.g. at [0003]; [0046]-[0048]. Baltz also describes daptomycin as a fermentation product, and Baltz is referred to in the Patents as a means of general identification of daptomycin, rather than for its specific stereochemistry. The Patents are not concerned with the stereochemistry of daptomycin and none of them contain a stereochemical formula for daptomycin. This is confirmed by Figure 1 of the Patents, which shows the structure of daptomycin but not its stereochemistry.

380. Secondly, Hospira's argument is even weaker in respect of the Purity Patents than in respect of the 417 Patent. The Purity Patents refer to Baltz, but make no reference to Figure 1A.

381. Thirdly, Prof Davies, the stereochemistry expert for Cubist, pointed out that the steps needed to elucidate the stereochemistry of daptomycin at the priority date would have been particularly complex and lengthy, owing to the large number of chiral centres and the total number of possible isomers. He considered that the accuracy to which this could be determined at the priority date would have been low.

382. In particular, the constitutional ("gross") structure of daptomycin is shown in EP 179 and 047 and it would be apparent to the skilled reader that there were thirteen chiral centres which could potentially give rise to 213 individual stereoisomers. An in vitro total synthesis of daptomycin would have been required to obtain any one of the possible stereoisomers, which would have presented a considerable task. It would have been pointless, as the skilled reader is told, and would know, that daptomycin can simply be obtained by fermentation. This indicates that the stereochemistry of daptomycin is a complexity which it is unnecessary for the skilled person to investigate and understand in order to put the teaching of the Patents into practice.

383. Fourthly, the evidence was that the skilled team would be able to manufacture, isolate and test daptomycin produced by fermentation of Strepomyces roseosporus, as real teams were able to do precisely that, in spite of the mistaken assignment in Fig 1A of Baltz, and before the correction was made by Miao in 2005. Dr Zeckel explained that Lilly had been working with daptomycin since 1985 and the mistaken assignment of the stereochemistry did not stop the work on daptomycin that was carried out post-Baltz and pre-Miao. Daptomycin made before 2005 by fermentation was no different to daptomycin made after 2005 by the same process. After 2005 the understanding of the stereochemistry of the 2Asn had changed, but that made no difference to the

ability of skilled persons to produce and isolate daptomycin, and to administer it to patients.

384. Finally, the exact stereochemical assignment of daptomycin was not necessary information to work the invention, as the Patents enable daptomycin to be made. This was the view of Prof Davies, which I accept, and which he expressed, for example at T2/162/17-163/9:

> "Q. Right, for reasons we have been discussing, it might be important to the biological activity.
>
> A. I do not think that is true. They have isolated a natural product that they know is essentially a single compound. They know that it has a certain set of biological activities which are useful to them. They know that they can reproduce the production of this compound. It is going to be a useful thing whether they know the structure or not. If it is there, they might go and have a look.
>
> Q. I think you are saying that they would go and have a look and that is to do with the stereochemistry and I am trying to explore with you why they would be interested in the stereochemistry.
>
> A. Well, I hoped they are chemists who were interested in all forms of stereochemistry. It does not mean it affects their compound or the way it is made or the way it is isolated. Or the way it can be used."

385. Prof Barrett accepted that the correct stereoisomer of daptomycin would dilute with a distinctive signature peak in an HPLC separation; T2/100/19-101/5. Therefore, the skilled team could have confirmed, had it wished to do so that it had isolated daptomycin without needing to know its precise stereochemical assignment.

386. I should add that Cubist advanced an alternative case that, as Baltz was a review paper, if the skilled person was interested in stereochemistry, he would have gone back to the primary literature and read a paper by Debono, from which he would have realised that Baltz had incorrectly reported the stereochemistry of daptomycin. Had I otherwise considered that the Patents were insufficient, I would not have accepted this argument. It led to a dispute of spiralling complexity between the experts, the result of which is that I accept Prof Barrett's evidence that Debono does not show, with any degree of clarity, that Baltz was wrong.

Conclusions

387. My conclusions in relation to the 417 Patent are as follows:

i) The 417 Patent is not entitled to its first claimed priority date, but is entitled to its second claimed priority date.

ii) The 417 Patent is not anticipated by the Cubist Press Release. However, all of the claims alleged to be independently valid are obvious in the light of that press release.

iii) The 417 Patent is not anticipated by Woodworth. However, all of the claims alleged to be independently valid are obvious in the light of Woodworth.

iv) The claims as proposed to be amended do not add matter over the application as filed. However, claim 2 as proposed to be amended lacks clarity.

v) There is no squeeze between sufficiency of the 417 Patent and the prior art.

388. My conclusions in relation to the 179 Patent are as follows:

i) The 179 Patent lacks inventive step over US 843.

ii) Claim 1 (but not claims 3, 4 and 5) of the 179 Patent lacks inventive step over the common general knowledge alone.

iii) The claims of the 179 Patent do not add matter over the application as filed.

iv) If I had reached a different conclusion on added matter, I would have allowed the conditional amendments proposed by Cubist to the claims of the 179 Patent. These conditional amendments were not alleged to make, and would not have made, any difference to my conclusions concerning lack of inventive step.

v) The claims of the 179 Patent are enabled across their full width and there is no squeeze with the prior art

389. My conclusion in relation to the 047 Patent is that it lacks inventive step over Lin & Jiang.

390. My conclusion in relation to the alleged "daptomycin insufficiency" is that this challenge to validity fails against all of the Patents.

391. For these reasons, I have concluded that each of the 417, 179 and 047 Patents is invalid. Therefore, Hospira's claim for revocation is successful.