IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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|---|---|---|
| CUBIST PHARMACEUTICALS, INC., | ) | |
| | ) | |
| Plaintiff, | ) | |
| | ) | |
| v. | ) | C.A. No. 12-367-GMS |
| | ) | |
| HOSPIRA, INC., | ) | |
| | ) | |
| Defendant. | ) | |
| | ) | |

**MEMORANDUM OPINION**

## I. INTRODUCTION

In this patent infringement action, plaintiff Cubist Pharmaceuticals, Inc. ("Cubist") alleges that pharmaceutical products proposed by defendant Hospira, Inc. ("Hospira") infringe the asserted claims of the patents-in-suit. (D.I. 1.) The court held a five-day bench trial in this matter on February 18 through February 24, 2014. (D.I. 121–125.) Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the patents-in-suit and whether Hospira's proposed products infringe the patents-in-suit. (D.I. 126–28.)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that: (1) the Certificate of Correction issued for the RE'071 Patent is not invalid, and therefore Hospira's products infringe the RE'071 Patent; (2) the RE'071 Patent is not invalid for lack of written description; (3) the RE'071 Patent is not invalid for improper recapture; (4) a revision to the court's claim construction of the term "daptomycin" in the '967, '689, '238, and '342 Patents is not warranted, and therefore Hospira's products infringe the '967, '689, '238, and '342 Patents; (5) the '967, '689, '238, and '342 Patents are not invalid for lack of written description; (6) the asserted claims of the '967 Patent are invalid

due to anticipation; (7) the asserted claims of the '967 and '689 Patents are invalid due to obviousness; (8) claim 98 of the '238 Patent is invalid due to anticipation; (9) the asserted claims of the '238 and '342 Patents are invalid due to obviousness; (10) Hospira's § 102(f) derivation defense is untimely and precluded; and (11) each of the parties' Rule 52(c) motions are granted in part and denied in part. These findings of fact and conclusions of law are set forth in further detail below.

## II. FINDINGS OF FACT[1]

### A. The Parties

1. Plaintiff Cubist Pharmaceuticals Inc. ("Cubist") is a Delaware corporation having a principal place of business at 65 Hayden Avenue, Lexington, Massachusetts.

2. Hospira, Inc. ("Hospira") is a Delaware corporation having a principal place of business at 275 North Field Drive, Lake Forest, Illinois.

3. The court has subject matter jurisdiction, as well as personal jurisdiction over all parties.

### B. Background

4. Cubicin® (daptomycin for injection) is an intravenous bactericidal antibiotic approved by the Food and Drug Administration ("FDA") for the treatment of infections caused by certain Gram-positive bacteria, such as *Staphylococcus aureus*, including methicillin-resistant strains, also known as MRSA.

5. Cubicin® was approved for the treatment of complicated skin and skin structure infections in 2003. It was approved for the treatment of bloodstream infections (bacteremia), including right-sided infective endocarditis caused by MRSA, as well as by methicillin-susceptible *Staphylococcus aureus*, in 2006.

6. The '967 Patent, the '689 Patent, the RE'071 Patent, the '238 Patent, and the '342 Patent (described below) have been listed in connection with Cubicin® in the FDA's publication,

[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 109, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. Where necessary, the court has overruled objections to the inclusion of these facts. The court has also reordered and renumbered some paragraphs, corrected some spelling and formatting errors, and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in the Discussion and Conclusions of Law section of this opinion, preceded by the phrase "the court finds" or "the court concludes."

*Approved Drug Products with Therapeutic Equivalence Evaluations*, which is commonly referred to as the "Orange Book."

**C. The Patents-in-Suit**

7. U.S. Patent Number 6,468,967 ("the '967 Patent")—"Methods for Administration of Antibiotics"—issued on October 22, 2002. The '967 Patent is assigned to Cubist.

8. The '967 purports to claim priority to Provisional Application Number 60/101,828, filed on September 25, 1998, and to Provisional Application Number 60/125,750, filed on March 24, 1999.

9. The '967 Patent lists Frederick B. Oleson, Jr. and Francis P. Tally as inventors.

10. U.S. Patent Number 6,852,689 ("the '689 Patent")—"Methods for Administration of Antibiotics"—issued on February 8, 2005. The '689 Patent is assigned to Cubist.

11. The '689 Patent is a continuation of U.S. Application Number 09/406,568, now the '967 Patent, and purports to claim priority to Provisional Application Number 60/101,828, filed on September 25, 1998, and to Provisional Application No. 60/125,750, filed on March 24, 1999. The '689 Patent is subject to a terminal disclaimer.

12. The '689 Patent lists Frederick B. Oleson, Jr. and Francis P. Tally as inventors.

13. U.S. Patent Number 8,058,238 ("the '238 Patent")—"High Purity Lipopeptides"—issued on November 15, 2011. The '238 Patent is assigned to Cubist.

14. The '238 Patent claims priority to U.S. Application Number 10/747,485, filed on December 29, 2003, which is a division of U.S. Application Number 09/735,191, filed on November 28, 2000, now U.S. Patent Number 6,696,412, and Provisional Application Number 60/177,170, filed on January 20, 2000.

15. The '238 Patent lists Thomas Kelleher, Jan-Ji Lai, Joseph P. DeCourcey, Paul Lynch, Maurizio Zenoni, and Auro Tagliani as inventors.

16. U.S. Patent Number 8,129,342 ("the '342 Patent")—"High Purity Lipopeptides"—issued on March 6, 2012. The '342 Patent is assigned to Cubist.

17. The '342 Patent claims priority to U.S. Application Number 11/739,180, filed on April 24, 2007, now the '238 Patent, which is a continuation of U.S. Application Number 10/747,485, filed on December 29, 2003, which is a division of U.S. Application Number 09/735,191, filed on November 28, 2000, now U.S. Patent Number 6,696,412, and Provisional Application Number 60/177,170, filed on January 20, 2000. The '342 Patent is subject to a terminal disclaimer to the '238 Patent.

18. The '342 Patent lists Thomas Kelleher, Jan-Ji Lai, Joseph P. DeCourcey, Paul Lynch, Maurizio Zenoni, and Auro Tagliani as inventors.

19. U.S. Patent Number RE39,071 ("the RE'071 Patent")—"Anhydro- and Isomer-A-21978C Cyclic Peptides"—issued on April 18, 2006. The RE'071 Patent is assigned to Cubist.

20. The RE'071 Patent is a reissue of U.S. Patent Number 5,912,226 ("the '226 Patent").

21. The RE'071 Patent is a continuation of U.S. Application Number 07/670,375, filed on March 14, 1991, which is a continuation of U.S. Application Number 07/060,148, filed June 10, 1987.

22. The RE'071 Patent lists Patrick J. Baker, Manuel Debono, Khadiga Z. Farid and R. Michael Molloy as inventors

23. A Request for Certificate of Correction for the RE'071 Patent was filed on October 18, 2007, and a Certificate of Correction issued for the RE'071 Patent on January 29, 2008.

### 1. The Asserted Claims[2]

24. Cubist is asserting claims 16, 17, 34, and 35 of the '967 Patent.

25. Cubist is asserting claims 51 and 52 of the '689 Patent.

26. Cubist is asserting claims 91, 98, and 187 of the '238 Patent.

27. Cubist is asserting claims 23 and 53 of the '342 Patent.

28. Cubist is asserting claims 18 and 26 of the RE'071 Patent.

#### *a. '967 Patent, Claim 16*

29. Claim 16 of the '967 Patent reads:

> The method according to claim 14, [comprising the step of administering to a human patient in need thereof a therapeutically effective amount of daptomycin . . . at a dosage interval that minimizes skeletal muscle toxicity], wherein the dose is 4 mg/kg [repeatedly] administered once every 24 hours.

[2] Several of the asserted claims are dependent claims. For clarity, the court has included language from the unasserted claims on which they depend to offer a more complete view of what the claims cover.

*b. '967 Patent, Claim 17*

30. Claim 17 of the '967 Patent reads:

> The method according to claim 14, [comprising the step of administering to a human patient in need thereof a therapeutically effective amount of daptomycin . . . at a dosage interval that minimizes skeletal muscle toxicity], wherein the dose is 6 mg/kg [repeatedly] administered once every 24 hours.

*c. '967 Patent, Claim 34*

31. Claim 34 of the '967 Patent reads:

> The method according to claim 33 [for treating or eradicating a bacterial infection in a human patient in need thereof, comprising the step of administering a therapeutically effective amount of daptomycin . . . to the patient at a dosage interval that minimizes skeletal muscle toxicity, wherein the daptomycin dose is repeatedly administered at the dosage interval of once every 24 hours . . . until said bacterial infection is treated or eradicated], wherein the dose is 4 mg/kg.

*d. '967 Patent, Claim 35*

32. Claim 35 of the '967 Patent reads:

> The method according to claim 33 [for treating or eradicating a bacterial infection in a human patient in need thereof, comprising the step of administering a therapeutically effective amount of daptomycin . . . to the patient at a dosage interval that minimizes skeletal muscle toxicity, wherein the daptomycin dose is repeatedly administered at the dosage interval of once every 24 hours . . . until said bacterial infection is treated or eradicated], wherein the dose is 6 mg/kg.

*e. '689 Patent, Claim 51*

33. Claim 51 of the '689 Patent reads:

> The method according to claim 48 [for administering daptomycin, comprising the step of administering to a human patient in need thereof a therapeutically effective amount of daptomycin in a dose of at least 3 mg/kg of daptomycin at a dosage interval that minimizes skeletal muscle toxicity, wherein the dose is repeatedly administered

at a dosage interval of once every 48 hours], wherein the dose is 4 mg/kg.

*f. '689 Patent, Claim 52*

34. Claim 52 of the '689 Patent reads:

> The method according to claim 48 [for administering daptomycin, comprising the step of administering to a human patient in need thereof a therapeutically effective amount of daptomycin in a dose of at least 3 mg/kg of daptomycin at a dosage interval that minimizes skeletal muscle toxicity, wherein the dose is repeatedly administered at a dosage interval of once every 48 hours], wherein the dose is 6 mg/kg.

*g. '238 Patent, Claim 91*

35. Claim 91 of the '238 Patent reads:

> The method of claim 85 [for preparing a pharmaceutical composition comprising combining . . . a purified daptomycin composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin being obtained by a process comprising the step of forming an aggregate comprising daptomycin . . . with a pharmaceutically acceptable carrier or excipient], wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

*h. '238 Patent, Claim 98*

36. Claim 98 of the '238 Patent reads:

> The composition of claim 97, [wherein the purity of daptomycin is at least 93% . . . and the daptomycin is obtained by a process comprising:
>
> a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;
> b) separating the daptomycin aggregate from low molecular weight contaminants with ultrafiltration or size exclusion chromatography; and
> c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociates into daptomycin monomers;
>
> and further comprising separating the daptomycin monomers obtained from step c) from high molecular weight contaminants

with a size selection technique], wherein the size selection technique is ultrafiltration or size exclusion chromatography.

*i. '238 Patent, Claim 187*

37. Claim 187 of the '238 Patent reads:

The composition of claim 183, [for a purified daptomycin composition of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, wherein the percent purity is measured by HPLC analysis, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin], wherein the daptomycin composition is at least or about 97% pure.

*j. '342 Patent, Claim* 23

38. Claim 23 of the '342 Patent reads:

The pharmaceutical composition of claim 22, [compatible with a pharmaceutically acceptable carrier for the treatment of an infection of the blood, skin or soft tissue in a daily dose of 1 to 12 mg/kg, of daptomycin in a reconstituted solution of the composition in the pharmaceutically acceptable carrier, selected from the group consisting of physiological saline and Ringer's solution for intravenous administration as a single daily dose to the subject, wherein the daptomycin has greater than 93% purity, less than 4% anhydro daptomycin and less than 4% β-isomer of daptomycin; and the composition comprising daptomycin is obtained by a purification process comprising the steps of:

a) subjecting daptomycin to anion exchange chromatography to obtain an enriched daptomycin preparation
b) forming the daptomycin aggregate comprising a daptomycin micelle in the enriched daptomycin preparation or a composition obtained from the enriched daptomycin preparation; and
c) obtaining the daptomycin from the daptomycin aggregate],

wherein the daptomycin is obtained from the daptomycin aggregate by a method comprising the steps of

a) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and
b) collecting the daptomycin aggregate.

*k. '352 Patent, Claim 53*

39. Claim 53 of the '342 Patent reads:

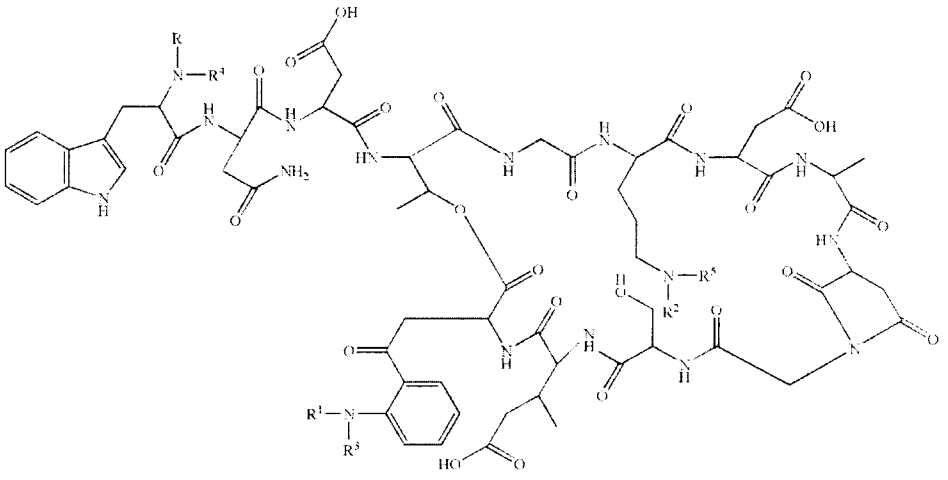
> The composition of claim 52 [obtained by a process comprising the steps of forming a daptomycin aggregate, converting the daptomycin aggregate to monomers and obtaining the daptomycin in the composition from the monomers by a process including one or more steps selected from the group consisting of anion exchange chromatography and hydrophobic interaction chromatography], wherein
>
> a) the composition is a lyophilized powder compatible with a pharmaceutically acceptable carrier for the treatment of an infection by a daily intravenous dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the lyophilized powder in the pharmaceutically acceptable carrier; and
>
> b) the daptomycin has a purity of about 94 to 96% relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin having less than 1% of the lactone hydrolysis product of daptomycin, less than 4% anhydro daptomycin and less than 4% of the β-isomer of daptomycin.

*l. RE'071 Patent, Claim 18*

40. Claim 18 of the RE'071 Patent reads:

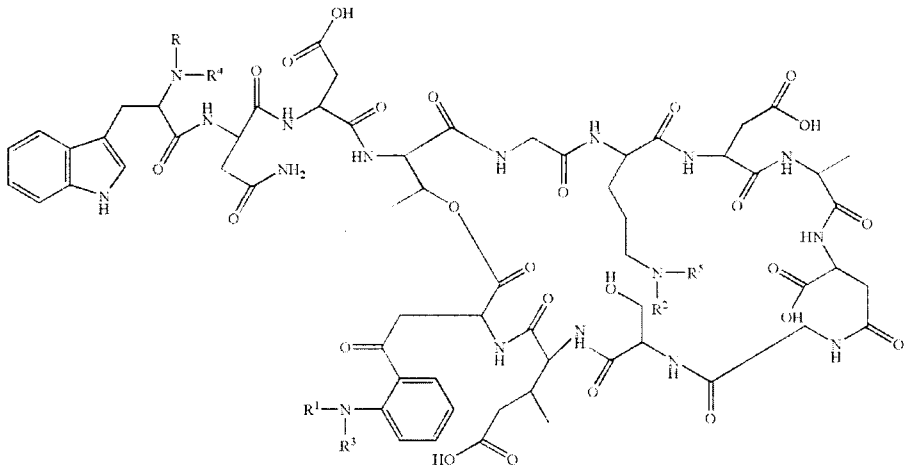
> An antibiotic composition comprised of a combination of a compound of formula 1, a compound of formula 2 and a compound of formula 3, or pharmaceutically acceptable salts thereof, wherein the formula 1 compound is

*FORMULA 1*



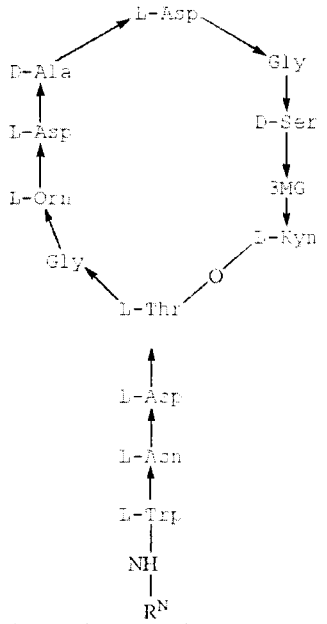
in which R is a $C_{10}$ alkanoyl; $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are hydrogen, and wherein the alanine is D-alanine and the serine is D-serine; the formula 2 compound is

*FORMULA 2*



in which R is a $C_{10}$ alkanoyl; $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are hydrogen, and wherein the alanine is D-alanine and the serine is D-serine; and the formula 3 compound is an A21978C cyclic peptide of

*FORMULA 3*




wherein $R^N$ is n-decanoyl; and wherein the total amount of the compound of formula 1 and the compound of formula 2, or salts thereof, in the combination is less than 6 weight percent.

*m. RE'071 Patent, Claim 26*

41. Claim 26 of the RE'071 Patent reads:

> A pharmaceutical formulation comprising a combination of a compound of formula 1, a compound of formula 2 and a compound of formula 3, or pharmaceutically acceptable salts thereof, wherein the formula 1 compound is [shown above] in which R is a $C_{10}$ alkanoyl; $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are hydrogen, and wherein the alanine is D-alanine and the serine is D-serine; the formula 2 compound is [shown above] in which R is a $C_{10}$ alkanoyl; $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are hydrogen, and wherein the alanine is D-alanine and the serine is D-serine; and the formula 3 compound is an A21978C cyclic peptide of [shown above] wherein $R^N$ is n-decanoyl; and wherein the total amount of the compound of formula 1 and the compound of formula 2, or salts thereof, in the combination is less than 6 weight percent, and the pharmaceutical formulation further comprises from about 0.1 to about 90 weight percent of the A21978C cyclic peptide of formula 3.

**D. Hospira's ANDA and NDA**

42. Hospira filed Abbreviated New Drug Application ("ANDA") No. 202857 with the FDA seeking approval for the commercial manufacture, use, and sale of daptomycin for injection, 500 mg/vial ("Hospira's Daptomycin ANDA Product") prior to the expiration of the '967, '689, RE'071, '238, and '342 Patents.

43. Hospira's ANDA includes a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that, *inter alia*, the '967, '689, RE'071, '238, and '342 Patents are invalid, are unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Hospira's Daptomycin ANDA Product.

44. By letter dated February 7, 2012 (the "Notice Letter"), Hospira notified Cubist that it had submitted ANDA No. 202587 to obtain approval to engage in the commercial manufacture, use, and sale of Hospira's Daptomycin ANDA Product prior to the expiration of, *inter alia*, the '967, '689, RE'071, and '238 Patents.

45. This action was commenced on March 21, 2012, before the expiration of forty-five days from the date of the receipt of the Notice Letter.

46. By letter dated May 31, 2012 (the "Second Notice Letter"), Hospira notified Cubist that it had submitted an amendment to the FDA for its previously submitted ANDA No. 202587 to obtain approval to engage in the commercial manufacture, use, and sale of Hospira's Daptomycin ANDA Product prior to the expiration of the '342 Patent.

47. Civil Action No. 12-859-GMS was commenced on July 9, 2012, before the expiration of forty-five days from the date of the receipt of the Second Notice Letter. Civil Action No. 12-859-GMS was consolidated with this action on August 31, 2012.

48. Hospira filed New Drug Application ("NDA") No. 203797 with the FDA under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, seeking approval for the commercial manufacture, use, and sale of Daptomycin for Injection, 350 mg/vial ("Hospira's 505(b)(2) Product"), prior to the expiration of the '967, '689, RE'071, '238, and '342 Patents.

49. By letter dated August 10, 2012 (the "505(b)(2) Notice Letter"), Hospira notified Cubist that it had submitted NDA No. 203797 to obtain approval to engage in the commercial manufacture, use, offer for sale, and/or sale of Hospira's 505(b)(2) Product prior to the expiration of, *inter alia*, the '967, '689, RE'071, '238, and '342 Patents.

50. In the 505(b)(2) Notice Letter, Hospira alleged that the '967, '689, RE'071, '238, and '342 Patents, *inter alia*, are invalid, are unenforceable, and/or will not be infringed by the commercial manufacture, use, offer for sale, or sale of Hospira's 505(b)(2) Product.

51. Civil Action No. 12-1142-GMS was commenced on September 17, 2012, before the expiration of forty-five days from the date of the receipt of the 505(b)(2) Notice Letter.

52. Civil Action No. 12-1142-GMS was consolidated with this action on October 19, 2012.

**E. Infringement**

53. Under the court's current claim construction, Hospira stipulated to infringement (active or induced) of the asserted claims of the patents-in-suit.[3]

**F. Certificate of Correction**

54. The Certificate of Correction for RE'071 (noted above) changed one amino acid in the tail portion of Formula 3 from L-Asn to D-Asn (reflecting different stereoisomer configurations of the amino acid asparagine).

55. The Certificate of Correction does not correct a clerical or typographical error.[4]

[3] Hospira reserved the right to argue non-infringement in the event that the court revised its claim construction order, concerning the construction of the term "daptomycin" and "Formula 3 compound," (D.I. 59), or if the court ruled the Certificate of Correction for the RE'071 patent was invalid. (D.I. 109 at 6–7.) These matters are discussed in detail below.

[4] As such, the dispute, discussed below, concerns whether the Certificate of Correction corrects a mistake of "minor character." 35 U.S.C. § 255.

## III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that: (1) the Certificate of Correction issued for the RE'071 Patent is not invalid, and therefore Hospira's products infringe the RE'071 Patent; (2) the RE'071 Patent is not invalid for lack of written description; (3) the RE'071 Patent is not invalid for improper recapture; (4) a revision to the court's claim construction of the term "daptomycin" in the '967, '689, '238, and '342 Patents is not warranted, and therefore Hospira's products infringe the '967, '689, '238, and '342 Patents; (5) the '967, '689, '238, and '342 Patents are not invalid for lack of written description; (6) the asserted claims of the '967 Patent are invalid due to anticipation; (7) the asserted claims of the '967 and '689 Patents are invalid due to obviousness; (8) claim 98 of the '238 Patent is invalid due to anticipation; (9) the asserted claims of the '238 and '342 Patents are invalid due to obviousness; (10) Hospira's § 102(f) derivation defense is untimely and precluded; and (11) each of the parties' Rule 52(c) motions are granted in part and denied in part. The court's reasoning follows.

### A. The RE'071 Patent

#### 1. Certificate of Correction

Hospira argues that the Certificate of Correction filed in 2007 for the RE'071 Patent is invalid because it did not correct a mistake of "minor character." *See* 35 U.S.C. § 255. Thus, Hospira contends that the asserted claims of the RE'071 Patent only cover compounds of "Formula 3" as it was originally identified, prior to correction, having an L-asparagine amino acid in the tail

portion of the chemical structure.[5] Because its proposed products possess D-asparagine instead, Hospira argues it does not infringe the RE'071 Patent.[6]

"[A] mistake the correction of which broadens a claim is not a 'mistake of . . . minor character.'" *Superior Fireplace Co. v. Majestic Prods. Co.*, 270 F.3d 1358, 1376 (Fed. Cir. 2001). And determining whether a claim is "broadened through correction requires interpreting the old and new versions of that claim, and then determining whether the new version covers territory the old one did not." *Cent. Admixture Pharmacy Servs., Inc. v. Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1353 (Fed. Cir. 2007). Indeed, a certificate of correction is invalid if the corrected claim "contains within its scope any conceivable apparatus or process which would not have infringed the original patent." *Tillotson, Ltd. v. Walbro Corp.*, 831 F.2d 1033, 1037 n.2 (Fed. Cir. 1987) (emphasis added) (discussing broadening in the context of patent reissue applications). A certificate of correction is part of a duly issued patent; therefore, "the party seeking invalidation must meet the clear and convincing standard of persuasion." *Cent. Admixture*, 482 F.3d at 1353 (internal quotation marks omitted).[7]

Both parties offer compelling arguments. On the one hand, Hospira is certainly correct that Formula 3 in the corrected RE'071 Patent is different from the pre-correction Formula 3. Focusing solely on the chemical structure identified in the claims, the court is presented with a clear case of claim broadening. On the other hand, as Cubist emphasizes, the court's focus is not limited to the

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[5] To avoid confusion, the court refrains from referring to these "Formula 3" compounds as "daptomycin," which, as discussed below, is known to possess D-asparagine.

[6] In the parties' Proposed Pretrial Order, Hospira stipulated that:

> Making, using, offering to sell, selling, or importing Hospira's Daptomycin ANDA and 505(b)(2) Products in/into the United States would directly infringe claims 18, 19, 26, and 28 of the RE'071 patent, unless such claims are found to be invalid, *the Certificate of Correction is found to be invalid*, or the Court's construction of "Formula 3 compound" is reversed.

(D.I. 109 at 8 (emphasis added).)

[7] "Clear and convincing evidence is evidence that places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Alza Corp v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

chemical structure. Cubist argues that the particular chemical structure of Formula 3 is just one of three ways the RE'071 Patent describes the compound of interest, as evidenced by the references to LY-146032 (Eli Lilly's codename for daptomycin) and A-21978C cyclic peptides (the byproduct of the *Streptomyces roseosporus* fermentation process). (D.I. 126 at 44.)

Ultimately the court finds that Hospira has not satisfied its heavy burden to show by clear and convincing evidence that the Certificate of Correction is invalid. Although the asserted claims of the RE'071 Patent make no explicit reference to a method of manufacture or source for the compound, there is mention of "an A21978C cyclic peptide of [Formula 3] wherein $R^N$ is n-decanoyl." Indeed the court's claim construction order confirmed that a "Formula 3 compound" is defined not just by the chemical structure but by this additional language as well.[8] (D.I. 59 at 3–4.) At the very least, the inclusion of both "an A21978C cyclic peptide . . ." and the chemical structure created an ambiguity requiring additional analysis of the specification. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 347 F.3d 1367, 1371 (Fed. Cir. 2003) ("[C]laims must be construed so as to be consistent with the specification, of which they are a part."); *see also Regents of Univ. of N.M. v. Knight*, 321 F.3d 1111, 1122 (Fed. Cir. 2003) ("[A] chemical structure is simply a means of describing a compound; it is not the invention itself.") Hospira has not shown that one skilled in the art, after examining the specification, still would have focused solely on the chemical structure identified in Formula 3—indeed, Hospira's expert Dr. Ganem did not consider the specification at all. (Tr. at 164 (Ganem).) Thus, even assuming that there was no excuse for why the incorrect stereochemistry was included in the original patent, the court applies the established legal standard

[8] The court's claim construction order assumed the validity of the Certificate of Correction and construed "Formula 3 compound" as having the corrected Formula 3, *i.e.*, with D-asparagine. (D.I. 59 at 3–4 & n.2.) The court deferred ruling on the question of the Certificate of Correction's validity until summary judgment. (*Id.* at 4 n.2.) Then, in its order denying Hospira's letter request to file summary judgment, the court stated that the issue would be best addressed at trial. (D.I. 107 at 2.)

that one skilled in the art would look to the entire specification to determine what was covered by the claims. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313–14 (Fed. Cir. 2005); *Merck*, 347 F.3d at 1371. The specification confirms that the Formula 3 compound identified in the claims is truly D-asparagine daptomycin, the byproduct of the fermentation process. Substituting L-asparagine for D-asparagine in the Formula 3 chemical structure was therefore a correction of minor character because it did not result in "the new version cover[ing] territory the old one did not." *See Cent. Admixture*, 482 F.3d at 1353. D-asparagine daptomycin was covered both before and after correction. The court finds the Certificate of Correction is valid, and Hospira infringes the RE'071 Patent.

**2. Written Description**

Hospira argues that, if the Certificate of Correction is valid, the RE'071 Patent is still invalid for failing the written description requirement imposed by § 112.

To satisfy the written description requirement, the application must show that, as of the filing date, the applicants were "in possession of the invention" in question. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991). "[T]he test for sufficiency is whether the disclosure of the application relied upon *reasonably conveys* to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (emphasis added). Although an exact definition of "possession" can be elusive, in essence, "the specification must describe an invention understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed." *Id.* To this end, support in the written description must be based on what actually is disclosed, and not on an obvious variant of what is disclosed. *See id.* at 1352 (citing *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997)). Whether the written description

requirement is met is a question of fact. *Id.* at 1351 (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985)). The party challenging the sufficiency of a written description must establish by clear and convincing evidence that the claim is invalid or not entitled to an asserted filing date. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1329–30 (Fed. Cir. 2008).

Hospira contends that one skilled in the art, reading the specification, would not know that the inventors were in possession of the D-asparagine daptomycin as of the filing date because the chemical structure indicated that L-asparagine compound was the subject of the invention. Hospira's argument rests, however, on the same flawed premise discussed above in the context of the Certificate of Correction. While it is true that Formula 3 (containing L-asparagine) would not have reasonably conveyed that the true structure contained D-asparagine (Tr. at 834 (Gerwick)), one skilled in the art would not have looked solely to the chemical structure to identify what had been invented. Rather, one skilled in the art would have understood that the inventors possessed and were working with the naturally occurring daptomycin molecule (containing D-asparagine), the fermentation byproduct. (Tr. at 186–87 (Ganem); Tr. at 825–26 (Gerwick).) Hospira has failed to show by clear and convincing evidence that the RE'071 Patent is invalid for lack of written description.

**3. Improper Recapture**

Hospira contends that the RE'071 Patent is invalid because the patentee surrendered subject matter during prosecution of the original '226 Patent that was later recaptured in the asserted claims of the reissue: the RE'071 Patent. In particular, Hospira points to cancelled claim 24 in the '226 Patent, which claimed a composition of "substantially pure" daptomycin. (DTX-532 at 53.) The specification indicated that "substantially pure" daptomycin contained less than 2.5% of additional

derivatives (Formula 1 and Formula 2 compounds). Hospira argues claim 24 was cancelled to overcome a prior art rejection. Hospira maintains that the asserted claims 18 and 26 of the RE'071 Patent improperly recapture the same disallowed subject matter.

"The recapture rule prevents a patentee from regaining through reissue the subject matter that he surrendered in an effort to obtain allowance of the original claims." *Yoon Ja Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1322 (Fed. Cir. 2006) (quoting *Pannu v. Storz Instruments, Inc.*, 258 F.3d 1366, 1370–71 (Fed. Cir. 2001) (internal quotation marks omitted). In applying the recapture rule:

> The first step is to determine whether and in what aspect the reissue claims are broader than the patent claims. The second step is to determine whether the broader aspects of the reissued claim related to surrendered subject matter. Finally, the court must determine whether the reissued claims were materially narrowed in other respects to avoid the recapture rule.

*Id.* at 1322 (quoting *Pannu*, 258 F.3d at 1371). As with other issues of patent validity, the challenger must establish improper recapture of subject matter by clear and convincing evidence. *Id.* at 1322.

The court finds that Hospira has failed to meet this burden. The cancelled claim 24 of the '226 Patent was directed to an anti-bacterial composition comprising daptomycin in substantially pure form; it did not require the inclusion of additional derivatives such as the Formula 1 or Formula 2 compounds. In contrast, the asserted claims of the RE'071 Patent are to a composition comprising each of the compounds of Formula 1, Formula 2, and Formula 3. Such elements are *required*, even if only in small amounts. Thus, the asserted claims of the RE'071 Patent are narrower than the cancelled claim 24, and they are not barred by the recapture rule. The court is not persuaded by Hospira's unsupported assertion that the recapture rule should apply because there was "no material narrowing." (D.I. 128 at 38.) Hospira has failed to show by clear and convincing evidence that the RE'071 Patent is invalid for improper recapture.

**B. Claim Construction Revision**

Hospira argues that the court should revise its construction of the term "daptomycin" as used in the '967, '689, '238, and '342 Patents. Specifically, Hospira asserts the same position it held previously that "daptomycin" should be construed according the stereochemistry of the amino acids that comprise the compound. Hospira argues that the court was misinformed that "new technology" was required to determine the precise stereochemistry and amino acid makeup of daptomycin, thus warranting a revision to the claim construction. If the court were to revise its construction to focus on the incorrect stereochemistry containing L-asparagine instead of D-asparagine (as discussed above), Hospira argues that its proposed products would not infringe the patents-in-suit.

The court's construction of claim terms need not be static. "[D]istrict courts may engage in a rolling claim construction, in which the court revisits and alters its interpretation of the claim terms as its understanding of the technology evolves." *Pressure Prods. Med. Supplies, Inc. v. Greatbatch Ltd.*, 599 F.3d 1308, 1316 (Fed. Cir. 2010) (quoting *Pfizer, Inc. v. Teva Pharm., USA, Inc.*, 429 F.3d 1364, 1377 (Fed. Cir. 2005)). Moreover, although there may be "the potential for surprise and prejudice in a late adjustment to the meaning of claim terms, . . . the trial court is in the best position to prevent gamesmanship and unfair advantage during trial." *Id.* at 1315. For bench trials, the court need not be concerned about confusing the jury with late changes to claim construction.

The court is not convinced, however, that a revision to its previous construction of "daptomycin" is justified. Hospira spent considerable time at trial offering evidence that the technology necessary to determine the proper stereochemistry of daptomycin was not "new technology," as stated in the court's claim construction order. (Tr. at 128–29 (Ganem).) But the

court's claim construction order did not rest on this issue—what Hospira calls a "false 'equitable' appeal." (D.I. 128 at 50.) Rather, the court's construction was based on the intrinsic evidence:

> [N]either the claim language nor the patent specification identifies the stereochemistry of daptomycin's amino acids. Rather, the specification refers to daptomycin as the natural product obtained from fermentation of Streptomyces roseosporus, which is the fermentation of bacteria. . . . The defendants' attempt to construe daptomycin as defined by its stereochemistry—and the wrong stereochemistry for the asparagine amino acid—when the claim language and specification does not do so, is inappropriate.

(D.I. 59 at 2 n.1.) The order goes on to cite additional intrinsic evidence supporting the construction as adopted. Hospira has not challenged the court's interpretation of this intrinsic evidence. Even if the court were to accept Hospira's arguments that the correct stereochemistry should have been determined at a much earlier date, Hospira fails to persuade the court that its original construction of daptomycin is no longer appropriate. The court will not revise its construction of daptomycin, and therefore Hospira infringes the '967, '689, '238, and '342 Patents.[9]

### C. Dosing Patents: The '967 and '689 Patents

The '967 and '689 Patents—referred to as the "dosing patents"—claim methods of administering daptomycin to patients, specifying dosage levels and intervals. Hospira contends that the '967 Patent is invalid as anticipated and that the asserted claims of both dosing patents are invalid as obvious. The court addresses each of these validity challenges.

#### 1. Anticipation

Hospira argues that the '967 Patent is anticipated by two prior art references: the Woodworth article and U.S. Patent Number 5,912,226 ("the '226 Patent").

[9] As with the RE'071 patent, Hospira contends that if the construction of daptomycin is retained, the '967, '689, '238, and '342 patents are invalid for lack of written description. Hospira makes the same arguments that the court rejected above. Hospira has not shown by clear and convincing evidence that one skilled in the art would have been unable to identify what the inventors of these four patents possessed. The intrinsic evidence provides ample support that "daptomycin," as used in the claims, was the natural byproduct of the fermentation of *Streptomyces roseosporus*.

"[I]nvalidity by anticipation requires that the four corners of a single[] prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). In *Verizon Services Corp. v. Cox Fibernet Virginia, Inc.*, the Federal Circuit discussed the standards for inherent disclosure:

> [A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. However, a patent claim cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112. It is well-settled that utility or efficacy need not be demonstrated for a reference to serve as anticipatory prior art under section 102.

602 F.3d 1325, 1337 (Fed. Cir. 2010) (alteration in original) (internal quotation marks and citations omitted).

A patent is presumed to be valid. 35 U.S.C. § 282. The party asserting invalidity bears the burden of establishing invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238 (2011). This burden of proof remains constant, even when a patent invalidity attack relies on the same prior art previously considered by the PTO. *See Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("The burden does not suddenly change to something higher—'extremely clear and convincing evidence' or 'crystal clear and convincing evidence'—simply because the prior art references were considered by the PTO.") Practically speaking, however, "it may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already

considered." *Id.* Whether a prior art reference anticipates a patent claim is a question of fact. *Advanced Display Sys.*, 212 F.3d at 1281.

In essence, the asserted claims of the '967 Patent require: (1) administering daptomycin, (2) to a human patient in need thereof, (3) repeatedly, (4) at a dosage interval of once every 24 hours, (5) wherein the dose is 4 mg/kg (claims 16 and 34) or 6 mg/kg (claims 17 and 35), and (6) wherein the dose minimizes skeletal muscle toxicity.

**a. Woodworth Article**

The Woodworth reference is a research article published in 1992; the parties do not dispute that it constitutes prior art, available before the priority date of the '967 Patent. The reference was cited to the PTO during prosecution.

Hospira argues that the Woodworth article discloses (to at least some degree) each of the elements of the asserted claims in the '967 Patent and therefore anticipates the '967 Patent. Although the studies, which are the subject of the research article, do not cover the claimed elements, Hospira argues that recommendations made by the reference constitute sufficient disclosures to enable and anticipate. Hospira points to a specific passage in the Abstract: "On the basis of the drug's [daptomycin's] pharmacokinetics and antibacterial activity, doses of 4 to 6 mg/kg/day, possibly in divided doses, are predicted to be effective." (DTX-427 at Abstract.) Hospira contends that this sentence is a sufficient disclosure to anticipate the '967 Patent. Even though there is no mention of minimizing skeletal muscle toxicity, Hospira argues this property would be an inherent consequence of following the other elements, thus satisfying the standard for anticipation. Cubist counters that the Woodworth disclosures (1) would not enable one skilled in the art to practice the invention, and (2) do not inherently minimize skeletal muscle activity.

The court notes initially that several of Cubist's counterarguments as to why the Woodworth article does not anticipate are more appropriately directed at an obviousness inquiry. Questions concerning the motivations of one skilled in the art, or whether the Woodworth article teaches away from the '967 Patent do not weigh on anticipation. *See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001) ("[A] reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." (quoting *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998))); *see also Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("The tests for anticipation and obviousness are different. . . . [O]bviousness requires analysis of secondary considerations of nonobviousness, while secondary considerations are not an element of a claim of anticipation.").

Turning first to the question of whether the Woodworth article discloses all of the claimed elements, the court notes that Cubist also spends considerable time discussing the experiments conducted in the Woodworth article, rather than focusing on the particular disclosure at issue, which was a prediction or suggestion for future study. But Hospira is correct that "anticipation does not require actual performance of suggestions in a disclosure." *See Bristol-Myers Squibb*, 246 F.3d at 1379. Thus, the only element Cubist contests is whether the Woodworth article inherently discloses "minimizing skeletal muscle toxicity." The court finds that it does. Regardless of whether one skilled in the art would be aware of it, following the suggestion disclosed by the Woodworth article (4–6 mg/kg/day) would have the physiological effect of minimizing skeletal muscle toxicity. (Tr. at 1028 (Guglielmo).) This cause-and-effect was the same at the time of the '967 priority date as it was when the Woodworth article was published. Cubist's expert Dr. Guglielmo conceded that he

had difficulty grasping the concept of inherent disclosures when multiple suggestions are offered in the prior art reference. (*Id.* at 1028–32.) Nonetheless, the law is clear that the "disclosure of multiple examples" does not "render[] one example less anticipatory." *Leggett & Platt, Inc. v. VUTEk, Inc.*, 537 F.3d 1349, 1356 (Fed. Cir. 2008). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). The court finds that minimizing skeletal muscle toxicity was a necessary accompaniment to the other disclosed claimed limitations and therefore was inherently disclosed by the Woodworth article.

Cubist's primary argument, however, is that, even if Woodworth discloses the necessary elements of the '967 Patent claims, they are not enabled by the disclosure. "An anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). The patentee, however, bears the burden of overcoming the presumption of prior art enablement by a preponderance of the evidence. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355–56 (Fed. Cir. 2003).[10] In overcoming this presumption, the patent holder should address several factors: the quantity of experimentation that was actually needed, the amount of guidance provided in the reference, the presence or absence of actual examples of the experimental

[10] Although it concedes that prior art *patents* have a presumption of enablement, Cubist argues there should be no presumption of enablement for prior art *printed publications*. (D.I. 126 at 8 n.7.) The Federal Circuit in *Amgen* never squarely addressed this question, although it indicated that there should be no distinction between patents and printed publications. *See Amgen*, 314 F.3d at 1355 n.22 ("We note that by logical extension, our reasoning here might also apply to prior art printed publications as well, but as Sugimoto is a patent we need not and do not so decide today."). The court finds this logical extension appropriate. Whereas the claims of a valid patent must be enabling by statute, 35 U.S.C. § 112, the additional disclosures in the specification need not. *Amgen* nonetheless held that both the claimed and unclaimed disclosures are presumed enabling. *Id.* at 1355. The court finds that printed publications should receive the same treatment as unclaimed disclosures. Moreover, patent examiners already apply a presumption of enablement to printed publications during the prosecution process. *See In re Antor Media Corp.*, 689 F.3d 1282, 1289 (Fed. Cir. 2012).

procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology. *See id.* at 1085.

Cubist presents arguments for each of the identified factors that the Woodworth article disclosure was not enabling.[11] Cubist asserts that the article presented findings for tests conducted on healthy individuals, and therefore it provides little guidance on how to formulate a clinical study on patients in need of therapy. The testimony offered by Dr. Guglielmo at trial indicated that designing a dosing regimen for clinical use was a complicated process, dependent on a number of variables—variables that the brief disclosure in the Woodworth article fails to identify. (Tr. at 959 (Guglielmo).)

The court is not convinced, however, that the Woodworth article was not enabling or that undue experimentation would be needed. Woodworth identified *the exact* dosage amounts and interval claimed by the '967 Patent: 4 mg/kg/day and 6 mg/kg/day. Even if one skilled in the art would have had to optimize other parameters to realize an effective clinical study, the dosage level and timing were two major variables that required no additional experimentation. The evidence adduced at trial demonstrated that the time it took to actually develop an effective clinical study of daptomycin was not solely attributable to scientific difficulties, but also commercial and business pressures. (Tr. at 675–78 (Eisenstein).) The court finds that Cubist has failed to rebut the presumption that the Woodworth article enabled the disclosed invention.

The novelty requirement of patent law embodies the policy that private entities should not be able to obtain patents "whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available." *See Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989) (quoting *Graham v. John Deere Co. of Kan. City,* 383 U.S.

[11] Hospira did not devote any of its post-trial briefing to discussing or rebutting Cubist's non-enablement argument.

1, 6 (1966)). The court finds that Hospira has demonstrated by clear and convincing evidence that the Woodworth article disclosed each of the elements of the claims of the '967 Patent, expressly or inherently. Cubist has not shown by a preponderance of the evidence that the Woodworth article was not enabling. Thus, Woodworth anticipates the '967 Patent and renders it invalid, pursuant to 35 U.S.C. § 102.

**b. '226 Patent**

Hospira also argues that the '226 Patent anticipates the asserted claims of the '967 Patent. The '226 Patent was filed in 1987, and the parties do not dispute that it qualifies as relevant prior art. The parties dispute the same issues as with the Woodworth reference.

Hospira points to a disclosure in the '226 Patent that "[a] typical daily dose for an adult human is from about 100 mg to about 1.0 g. . . . In practicing this method, the antibiotic compound can be administered as a single daily dose or in multiple doses per day . . . ." (DTX-002, col 10 ll. 57–61.) The experts agreed that this range, when using an average 70 kg human subject, corresponds to 1.4 mg/kg/day to 14 mg/kg/day. (Tr. at 276–77 (Ebert); Tr. at 1043–1044 (Guglielmo). Within this range fall the claimed dosage levels of 4 mg/kg/day and 6 mg/kg/day. Thus, Hospira argues that the '226 Patent anticipates the asserted claims of the '967 Patent.

The court finds that each of the claimed elements are disclosed in the '226 Patent. Cubist makes the same argument concerning minimizing skeletal muscle toxicity, discussed above in the context of the Woodworth article. The court rejected the argument above and does so again. Regardless of whether one skilled in the art knew it, the '226 Patent disclosed dosage levels that have the effect of minimizing skeletal muscle toxicity. The fact that the reference also disclosed dosage levels that do not have this effect does mean it cannot anticipate. *See Leggett & Platt*, 537 F.3d at 1356; *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) ("This

court rejects the notion that one of these ingredients cannot anticipate because it appears without special emphasis in a longer list.").

The court strays from its previous analysis, however, in finding that the disclosure in the '226 Patent is not enabling and therefore not anticipatory. *See Perricone*, 432 F.3d at 1376 ("[T]he disclosure is prior art to the extent of its enabling disclosure.") Whereas the Woodworth reference disclosed the precise dosage levels ultimately claimed, the '226 Patent provided a broad range of possibilities. Therefore, in addition to optimizing the variety of parameters necessary to design an effective clinical study, one skilled in the art would have had to test the various dosage levels, for daily and multiple dosing intervals. The '226 Patent offers no indication that 4 mg/kg/day or 6 mg/kg/day would have been preferable over the other possibilities, and the court is not convinced that one skilled in the art would have focused solely on the integer dosages levels to arrive at the claimed levels. (Tr. at 992 (Guglielmo).) Cubist has satisfied its burden in rebutting the presumption of enablement. The disclosure would have required undue experimentation, and it is not enabling. Therefore, the '226 Patent does not anticipate.

**2. Obviousness**

Hospira challenges the validity of each of the asserted claims of the '967 and '689 Patents as obvious in light of the prior art. The court finds, for the reasons that follow, that the defendants have established by clear and convincing evidence that the patents-in-suit are obvious.

35 U.S.C. § 103(a) provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact is directed

to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence" that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. As discussed above, this burden of proof remains constant, even when a patent invalidity attack relies on the same prior art previously considered by the PTO; still, "it may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered." *See Sciele Pharma*, 684 F.3d at 1260. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *See KSR*, 550 U.S. at 415. The *KSR* Court acknowledged, however, the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does in an obviousness determination." *Takeda Chem. Indus. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1356–57 (Fed. Cir. 2007) (quoting *KSR*, 550 U.S. at 418) (internal quotation marks omitted).

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

A finding that a patent is anticipated under § 102 often—but not necessarily—indicates that the patent is obvious under § 103. *Cohesive Techs.*, 543 F.3d at 1364 & n.2 (Fed. Cir. 2008) ("[O]ur precedent has rejected reliance on the 'legal homily' that 'anticipation is the epitome of obviousness.'" (quoting *Mendenhall v. Cedarapids, Inc.*, 5 F.3d 1557, 1563 (Fed. Cir. 1993))).

> The tests for anticipation and obviousness are different. Obviousness can be proven by combining existing prior art references, while anticipation requires all elements of a claim to be disclosed within a single reference. Moreover, obviousness requires analysis of secondary considerations of nonobviousness, while secondary considerations are not an element of a claim of anticipation. And although anticipation can be proven inherently, proof of inherent anticipation is not the same as proof of obviousness.

*Id.* at 1364 (internal citations omitted). Therefore, although the court found the '967 Patent to be anticipated, a separate obviousness analysis is still required.

**a. Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art[12]**

Hospira contends that the Woodworth article and the '226 Patent, in light of the known properties of daptomycin, render the asserted claims of the '967 and '689 Patents obvious. Cubist does not dispute that the Woodworth article and the '226 Patent are relevant prior art, but contends that they do nothing to suggest to one skilled in the art that claimed invention would have obvious.

As discussed above, the Woodworth article and the '226 Patent contained disclosures indicating that the claimed dosage levels would be effective, either through daily or divided administrations. Not relying solely on these disclosures, Hospira provides additional support for why one skilled in the art would find daily dosing preferable and obvious. Hospira points to four known qualities of daptomycin, which, it argues, illuminate the obviousness inquiry. First, daptomycin's effectiveness is concentration dependent, meaning the higher the concentration of daptomycin in the blood, the "better the killing." (Tr. at 1041 (Guglielmo).) Therefore, Hospira argues one skilled in the art would lean toward less frequent, more concentrated treatments, rather than divided dosages. This conclusion supports a daily dosing schedule.

Second, Hospira notes daptomycin's longer half-life; it acts in the body over an extended period before being cleared. Hospira contends that one skilled in the art would try to avoid administering new doses while prior dosages were still active, again supporting a daily dosing model. (Tr. at 243–44 (Ebert).) Third, and relatedly, Hospira argues that daptomycin has a long post-antibiotic effect—it continues to suppress bacteria after leaving the body—reducing the need to administer it repeatedly. (Tr. at 313–14 (Ebert); Tr. at 1089 (Guglielmo).)

[12] The parties do not appear to dispute the level of ordinary skill in the art. Therefore the court does not address this factor.

Finally, Hospira notes that skeletal muscle toxicity resulting from daptomycin (or other drugs) was known to be reversible in most cases. (Tr. at 326 (Ebert); Tr. at 1083–84 (Guglielmo).) Therefore, dosages spaced further apart—such as daily dosing—would allow the muscle more time to repair before the next dose, reducing the cumulative toxic effect.

In further support for its position, Hospira argues that known properties of a class of antibiotics known as aminoglycosides also would have indicated to one skilled in the art that daily dosing for daptomycin would have a reasonable probability of success. Hospira points to several shared properties of daptomycin and aminoglycosides, such as concentration-dependent killing, long post-antibiotic effects, and reversible toxicity. (Tr. at 319 (Ebert); Tr. at 1082–89 (Guglielmo).) Cubist disputes that one skilled in the art would look to aminoglycosides as relevant prior art for the purpose of assessing obviousness. Cubist emphasizes that aminoglycosides are structurally dissimilar, they cause toxicity in kidney and ear cells rather than skeletal muscle, and they exhibit low protein binding. (Tr. at 1006–09 (Guglielmo).)

The court agrees with Hospira that the body of knowledge concerning aminoglycosides is within the relevant prior art and would have been considered by one skilled in the art. Notwithstanding the chemical and biological differences highlighted by Cubist, the court finds that the *practical* difficulties presented by daptomycin would have encouraged one skilled in the art to look to other classes of antibiotics for ideas on how to resolve those difficulties.

Ultimately, the court finds that Hospira has established a *prima facie* case that the '967 Patent was obvious in light of the prior art. As stated above in the context of anticipation, the Woodworth article and the '226 Patent offered the base elements of the claimed invention. The additional knowledge and prior art available to one skilled in the art, however, further convinces

the court that one skilled in the art would have had a reasonable expectation of success. The cited references did not teach away from daily dosing or the other elements of the claims.

The court has not discussed the '689 Patent in detail thus far, but, in essence, it provides for dosages of daptomycin every 48 hours for patients with impaired renal function, rather than daily doses (every 24 hours). Hospira contends that these claims were logical extensions of the '967 Patent claims because one skilled art would recognize that patients with impaired renal function would not be able to clear daptomycin as efficiently. (Tr. at 1090 (Guglielmo).) As such, the dosing regimen would have to be adjusted from that of patients with normal kidney function, to avoid overdosing. The experts agreed that adjustments could be made to either the dosage level or the interval between doses. (Tr. at 332–35 (Ebert); Tr. at 1090–91 (Guglielmo).) Given daptomycin's concentration-dependent killing, one skilled in the art would have opted to increase the interval rather than sacrificing concentration. Therefore, for a patient with impaired kidney function (*e.g.*, 50% of normal function), an interval twice as long would have been obvious to one skilled in the art. Cubist's counterarguments rely primarily on their previous assertion that the daily doses for patients with normal functioning would not have been obvious. The court has explained that it disagrees with this position. Thus, Hospira has established its *prima facie* case that the '689 Patent was obvious as well.

**b. Secondary Considerations of Non-Obviousness**

The final factor in assessing obviousness is evaluating the objective indicia of non-obviousness, often referred to as secondary considerations. Cubist argues that the relevant considerations in this case are long-felt but unmet need, failure of others, unexpected results, and commercial success.

"Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer*, 480 F.3d at 1372. Moreover, "[a] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision." *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) (alteration in original) (quoting *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed. Cir. 2000)). In other words, the secondary considerations must be commensurate in scope—"coextensive"—with the claimed features of the invention. *Id.*; *see also MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264–65 (Fed. Cir. 2013).

Cubist argues there was a long-felt but unmet need for an effective daptomycin treatment regimen. Cubist points to prior failed studies conducted by Eli Lilly, attempting to treat *S. aureus* endocarditis ("SAE"). Eli Lilly researchers had seen some success treating other bacterial infections with daptomycin, but an effective treatment of SAE was the true goal. (Tr. at 576–78 (Zeckel).) Cubist argues that the embodiments of the claims of the '967 and '689 Patents addressed this long-felt need.

As Hospira points out, however, the claims of the '967 and '689 Patents are not truly commensurate with the long-felt need Cubist puts forth—treatment of serious infections like SAE. The claims cover bacterial infections generally. As Cubist's expert testified, Eli Lilly had previously been successful using daptomycin to treat some infections. (*Id.*) Moreover, vancomycin was the standard treatment for many of these same infections. (Tr. at 949–50 (Guglielmo).) Thus, for much of what the dosing patents claim, there was no long-felt need. *See Muniauction*, 532 F.3d at 1328 n.4 ("[C]laims which are broad enough to read on obvious subject matter are

unpatentable even though they also read on nonobvious subject matter." (quoting *In re Lintner*, 458 F.2d 1013, 1015 (C.C.P.A. 1972))).

These issues undermine Cubist's other secondary considerations as well. The weight of the "failure of others" factor becomes considerably more limited when it is acknowledged that others had only failed with respect to SAE. Additionally, whether or not Eli Lilly truly "failed" is a controversial matter: Eli Lilly owned and marketed vancomycin, the "gold standard" for treating many serious infections like MRSA. (Tr. 667–68 (Eisenstein).) Thus, economic considerations, and not merely difficulties in the lab, weighed on Eli Lilly's decision to "shelve" daptomycin development. (DTX-111 at 2; Tr. at 677–78 (Eisenstein).)

Evidence of commercial success is similarly weakened. Cubist presented figures demonstrating the success of its commercial embodiment, Cubicin. (D.I. 118.) But, as Hospira indicates, the commercial success must be tied to the merits of the claimed invention. *See Muniauction*, 532 F.3d at 1328 ("[C]ommercial success or other secondary considerations may presumptively be attributed to the patented invention only where the marketed product embodies the claimed features, and is coextensive with them."). For the reasons stated already, the nexus is strongest for the use of Cubicin to treat SAE only. But for Cubicin's use in other infections, which make up the majority of the market, Cubist was unable to establish that the claimed features drove market success. (Tr. 1108–09 (Murray).) The '967 and '689 Patents are *dosing* patents—they do not cover daptomycin itself. The court is not convinced that the dosing properties outlined in the claims are responsible for Cubicin's market success, as opposed to the "inherent properties" of daptomycin. (Tr. at 1132–37 (Rausser).)

Cubist also describes the unexpected results discovered by Dr. Tally and Dr. Oleson, that once daily dosing could be used to minimize skeletal muscle toxicity. The results were published

in several prestigious medical journals, and Cubist's expert Dr. Guglielmo testified that he was "very surprised." (PTX-33; PTX-47; Tr. at 951 – 52 (Guglielmo).) Once again, the court finds this factor is limited to serious infection applications like SAE. The claims of the dosing patents are not restricted to these infections; rather, they cover bacterial infections broadly.

Thus, there is a disconnect between what the dosing patents actually claim and the secondary considerations Cubist offers. The court is not convinced that the objective indicia cited by Cubist are entitled to significant weight; and any weight certain factors may have does not overcome Hospira's *prima facie* showing of obviousness. *See Muniauction*, 532 F.3d at 1327 ("[T]o the extent that some of the factors arguably meet the nexus requirement, their relationship to the claims is simply too attenuated to overcome the strong *prima facie* demonstration by Thomson that the claims are obvious."); *see also Pfizer*, 480 F.3d at 1372 ("Even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case."). Hospira has shown by clear and convincing evidence that the '967 and '689 Patents are obvious and therefore invalid under 35 U.S.C. § 103.

**D. Purity Patents: The '238 and '342 Patents**

The '238 and '342 Patents—referred to as the "purity patents"—claim methods of purification as well as daptomycin compositions purified via particular processes: product-by-process claims. *See SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1315 (Fed. Cir. 2006) ("A product-by-process claim is one in which the product is defined at least in part in terms of the method or process by which it is made." (internal quotation marks omitted)). "In determining validity of a product-by-process claim, the focus is on the product and not the process of making it." *Greenliant Systems, Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012) (quoting *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009)). Hospira contends (1)

that claim 98 of the '238 Patent is invalid as anticipated, (2) that the asserted claims of the purity patents are invalid as obvious, and (3) that the purity patents are invalid for lack of inventorship under § 102(f). The court addresses these validity challenges in turn.

**1. Anticipation**

Hospira argues that claim 98 of the '238 Patent is anticipated by U.S. Patent Number 4,874,843 ("the '843 Patent"). Claim 98 is a product-by-process claim covering purified daptomycin.

As explained before, a claim is anticipated where "a single[] prior art document describe[s] every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys.*, 212 F.3d at 1282. This rule applies for product-by-process claims as well, but the focus is always on the product itself: "an old product is not patentable even if it is made by a new process." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1366, 1370 (Fed. Cir. 2009) ("[A] product-by-process claim can be anticipated by a prior art product that does not adhere to the claim's process limitation."). An important exception to the rule, however, is where the process limitations impart "structural and functional differences" to the product, such that it is actually something "new." *Id.* at 1367. These structural and functional differences are relevant to the anticipation analysis, even where they are "not explicitly part of the claim[s]." *Id.* at 1370. The party asserting anticipation bears the burden of proving that the process limitations do not result in an invention distinguishable from the prior art. *Id.*

Hospira argues that the '843 Patent anticipates claim 98 of the '238 Patent. The '843 Patent discloses a method of purifying daptomycin, producing compositions having at most 93% purity, with respect to fourteen identified impurities. Similarly, Hospira argues, claim 98 of the '238 Patent

claims compositions having at least 93% pure daptomycin. Therefore, on its face, claim 98 appears to claim subject matter already disclosed in the prior art: compositions having daptomycin with 93% purity. As already stated, "a product-by-process claim can be anticipated by a prior art product that does not adhere to the claim's process limitation." *Id.* Therefore, the parties' dispute centers on whether the daptomycin composition produced via the claim 98 process limitations is structurally and functionally different from that disclosed by the '843 Patent.

Cubist argues that purification process outlined in the claim 98 results in a novel daptomycin composition because it results in the elimination of two types of impurities: endotoxins and saponins. Although the claims do not identify these impurities, Cubist argues the composition free from saponins and endotoxins is structurally and functionally different from the prior art composition. Essentially, Cubist contends the compositions are structurally different because these particular impurities were present (to some "measurable" degree) in the prior art and absent from the claim 98 composition. (Tr. at 778–82 (Gerwick).) In terms of functional difference, Cubist argues that a composition free from endotoxins and saponins is a safer product for the marketplace, and that a composition without saponins in particular allows for better purification. (Tr. at 777–80 (Gerwick)).

In response, Hospira (which bears the burden of proof) contends that there are not true functional differences between the '843 Patent daptomycin compositions and those claimed in claim 98. Hospira points to Eli Lilly clinical studies with purified daptomycin compositions, in which no toxicities were caused by endotoxins or saponins. (Tr. at 661 (Eisenstein).) Therefore, although, in theory, the presence of endotoxins and saponins could be harmful to patients (Tr. at 513–14 (Baker)), Hospira asserts that there is no meaningful functional difference because such impurities could be removed via known methods. Moreover, Hospira argues that the reduction of

saponin levels to improve purification is also not a true functional difference because the '843 Patent was already specifically aimed at removing saponins. (Tr. at 873–74 (Gerwick).) Hospira argues therefore that, even though the process recited in claim 98 may have reduced the content of endotoxins and saponins to a degree, as between these two composition, there are no functional differences in fact.

Claim 98 does not claim a daptomycin composition free from endotoxins and saponins. Had this property been expressly included in the claim, the anticipation analysis would be simple: does the '843 Patent teach the element? Because it is not claimed, the claim 98 product-by-process composition (free from endotoxins and saponins) must be structurally and functionally different from the '843 Patent compositions, such that it is something novel. *See Amgen*, 580 F.3d at 1366, 1370. The court finds that Hospira has satisfied its burden: daptomycin compositions purified pursuant to the claim 98 process limitations are not structurally and functionally different from those taught by the'843 Patent. Although endotoxins and saponins pose a risk to health when present in certain quantities, in reality Eli Lilly demonstrated (before Cubist) that purified daptomycin could be administered to patients without triggering toxicities from these impurities.[13] (Tr. at 661 (Eisenstein).) Moreover, although Cubists asserts that high endotoxin and saponin levels posed a problem initially (Tr. at 696, 706 (Kelleher)), at no point during the lengthy prosecution of the '238 Patent (and claim 98) did Cubist argue that eliminating these impurities distinguished claim 98 from the prior art. (Tr. at 843–44 (Gerwick).) Of course, as the court has stated, structural and functional differences from the prior art need not be explicitly claimed. *See Amgen*, 580 F.3d at

[13] Cubist makes much of the fact that there was little proof tying the Eli Lilly clinical studies to the process disclosed in the '843 Patent; Cubist therefore argues the clinical studies should be excluded from the anticipation analysis. (D.I. 126 at 31–32.) The court is not persuaded. Even if the methods were not identical, the clinical studies demonstrate that known purification methods could eliminate the health risks posed by endotoxins and saponins, such that their presence is not a true functional difference.

1370. But the court finds it telling that removal of endotoxins and saponins was never cited as a novel property of the invention.

The elimination of saponins to improve purification is also an illusory difference. After all, the '843 Patent already sought to improve purity by removing saponins. It is true that the claim 98 process limitations were able to yield even better saponin removal. (Tr. at 778–82 (Gerwick).) But this cannot qualify as a functional difference because the ultimate result is still a 93% pure daptomycin composition. In other words, the '843 Patent disclosed a method of purification (that remove some saponins) that yields 93% purity, whereas claim 98 claims a product-by-process (that removes *more* saponins) that also yields 93% purity.

Hospira has demonstrated by clear and convincing evidence that the product-by-process claimed in 98 is not patentably distinct from that taught by the '843 Patent. *See Amgen*, 580 F.3d at 1365–70. Thus, claim 98 is anticipated by the '843 Patent. Claim 98 is invalid.

**2. Obviousness**

Hospira argues that the asserted claims of the purity patents are both obvious in light of the prior art. The asserted claims of the purity patents cover two primary purification steps that Hospira contends are obvious: (1) micelle or aggregate filtration, followed by (2) anion exchange chromatography. As stated above, an obviousness inquiry depends on four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness. *See Graham*, 383 U.S. at 17–18. The parties do not appear to dispute the level of ordinary skill in the art, so the court focuses its discussion on the prior art and the secondary considerations.

**a. Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art**

*i. Micelle Filtration*

Hospira argues that micelle filtration would have been an obvious means of purifying daptomycin. As technical background, the purity patents describe the use of micelle filtration to separate the daptomycin molecules from impurities of different sizes. Under certain conditions (*i.e.*, at acidic pH), daptomycin forms micelles or aggregates. These aggregates effectively increase the size of the daptomycin, so that it is unable to pass through the pores of a filter. In contrast, smaller-molecule impurities (like saponins) can pass through the filter and can be discarded. Subsequently, by neutralizing the pH, the daptomycin aggregates would break apart into individual (smaller) molecules and pass through the filter's pores. Large molecules (like endotoxins) would remain blocked by the filter. This time, the filtrate containing daptomycin would be saved and whatever remained on the feed side of the filter could be discarded.

Cubist asserts that daptomycin's propensity to form micelles was unknown until discovered by the purity patents' inventors. Thus, Cubist argues, one skilled in the art would have had no reason to try micelle filtration, and therefore it could not have been obvious. Hospira responds that one skilled in the art would have looked to micelle filtration as an obvious mechanism for purifying daptomycin. First, Hospira argues that micelle filtration was a known purification process for a class of molecules known as surfactants. The Lin reference, published in 1997, demonstrated that it could be used to purify a molecule known as surfactin, and predicted that micelle filtration "can be further modified and employed for the recovery and purification of most surfactants." (DTX-345 at 416.) Second, Hospira argues that one skilled in the art would have recognized that daptomycin was a surfactant, prone to forming micelles. Hospira points to the Lakey reference from 1988, which observed that daptomycin displays concentration-dependent aggregation. (DTX-333 at

4643.) Lakey also disclosed that daptomycin moves toward the lipid-water interface. (*Id.*) Both of these properties, Hospira argues, would suggest to one skilled in the art that daptomycin is a surfactant, at a time prior to the priority date of the purity patents. Taking the Lin and Lakey references together, Hospira asserts that one skilled in the art would have found micelle filtration to be obvious.

The court is persuaded by Hospira's showing. The Lakey reference indeed taught one skilled in the art that daptomycin displayed the properties of a surfactant, even if these observations were not the primary goal of the research. Cubist's counterargument focuses on the fact that Lakey was an article discussing the antibacterial properties of daptomycin and was not concerned with purification. (Tr. at 804 (Gerwick).) Nonetheless, Lakey taught that daptomycin possesses these properties, and one skilled in the art would have recognized that the properties were characteristic of surfactants. At the very least, the court is convinced that one skilled in the art would have had a reason to believe that daptomycin was a surfactant and could have confirmed this suspicion with additional study, even without Lakey providing information on the conditions under which daptomycin displayed these properties.

Accepting that Lakey sufficiently taught that daptomycin was a surfactant, the court finds that Lin provides the remaining necessary disclosure. In unambiguous terms, Lin taught that micelle filtration "can be further modified and employed for the recovery and purification of most surfactants." (DTX-345 at 416.) Thus, even though Cubist identified numerous characteristics differentiating surfactin and daptomycin (Tr. at 797 – 800 (Gerwick)), Lin taught broadly that surfactants as a class can be purified with micelle aggregation. One skilled in the art would have realized that daptomycin is a surfactant and would have used micelle filtration as a means of purification. One skilled in the art would have been able to determine ideal conditions for forming

and breaking apart micelles with routine experimentation. (Tr. at 483–84 (Baker).) The court agrees with Hospira's *prima facie* obviousness showing with respect to micelle aggregation.

*ii. Anion Exchange Chromatography*

The second aspect of the purity patents in question is the anion exchange chromatography. Because micelle filtration only filtered impurities based on size, daptomycin-related substances—analogous molecules of similar size but slightly different chemistry—still remained in the filtrate. Cubist's expert Dr. Kelleher testified that many believed these substances could not be entirely removed because an equilibrium would always be established wherein daptomycin was converted into the analog forms as the impurities were removed. (Tr. at 702 (Kelleher).) Cubist asserts that, despite teachings in the '843 Patent that ion exchange chromatography was ineffective, the inventors of the purity patents discovered that ion exchange chromatography (specifically, anion exchange) could be used to further purify daptomycin, relative to daptomycin-related substances. (Tr. at 792–93 (Gerwick).)

Hospira again challenges Cubist's interpretation of the art. Hospira explains that ion exchange chromatography was known to be one of most common purification techniques in the field. (Tr. at 434–36 (Baker).) Moreover, Hospira explains that the '843 Patent did not teach away from using ion exchange chromatography as a purification technique for daptomycin, as argued by Cubist. Rather, the presence of saponins in the samples considerably "reduce[d] the effectiveness" of the ion exchange purification. (Tr. at 873–74 (Gerwick).) Therefore, rather than teaching away from ion exchange chromatography, the '843 Patent merely taught a method of removing saponins. (*Id.* at 874–75.) As Hospira explains, "the entire point of the '843 patent was to solve that problem." (D.I. 128 at 40.) That the '843 Patent did not go further than this first step of removing saponins does not mean it taught away from ion exchange chromatography.

The court agrees with Hospira and finds that anion exchange chromatography would have been an obvious method of purification to one skilled in the art, after solving the problem of removing saponins. As already explained, saponins could be removed using micelle filtration, as claimed in the purity patents, or using the process taught by the '843 Patent. After removing the saponins, one skilled in the art could apply the well-known ion exchange purification technique. The purity patents do not claim anything other than this simple concept. Indeed, as shown in Example 10 of the '342 Patent, running samples obtained via the '843 Patent process through an anion exchange column yielded a very high purity. (DTX-8, col 8–9; Tr. at 811–12 (Gerwick).) The fact that the '843 Patent did not run through this last step does not mean it was not obvious. Moreover, the court is not convinced that the industry "belief" that there was an "upper limit" on the purity of daptomycin possible would have discouraged one skilled in the art from applying a common purification technique after the saponin problem was resolved. (Tr. at 703–05 (Kelleher).)

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Hospira has established a *prima facie* case that both micelle filtration and anion exchange chromatography would have been obvious methods of purifying daptomycin to one skilled in the art. The court must take into account the secondary considerations of non-obviousness to determine whether this *prima facie* showing can be overcome.

**b. Secondary Considerations of Non-Obviousness**

Cubist cites long-felt but unmet need and unexpected results as objective indicia of non-obviousness. Hospira asserts that independent invention is an objective consideration weighing in favor of an obviousness finding. The court discusses these considerations briefly in turn.

For long-felt but unmet need, Cubist argues that the purity patents made possible the commercialization of daptomycin. Until Cubist's inventors developed their purification process,

the typical yields for daptomycin using existing methods were approximately 2%. (Tr. at 925 (Myerson).) Using the processes outlined in the purity patents, however, Cubist was able to obtain yields between 25% and 35%, making daptomycin a commercially viable drug for the first time. (*Id.* at 926.)

Hospira counters that there is no nexus between Cubist's asserted long-felt need and the actual claims of the purity patents. Hospira argues that the claims make no mention of commercialization or yield, broadly covering purification in a small lab setting or in a large-scale production plant. In other words, the claims are not truly commensurate with need cited by Cubist.

The court agrees with Hospira. As stated in the court's earlier discussion of secondary considerations, "[a] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision." *Muniauction*, 532 F.3d at 1327 (alteration in original). Although the processes described in the purity patents may have ultimately led to more efficient production, the claims themselves do not speak of yield. Rather, the claims cover highly pure daptomycin products, whether produced in an economical or wasteful manner. Moreover, Cubist appears to take as an established fact that a commercially viable method of producing daptomycin was long sought in the industry. But simply because prior efforts had seen lower yields does not necessarily mean there was a "need" for processes with higher yields. The court has already detailed some of the history of daptomycin's development. Indeed, elsewhere Cubist emphasized that many believed daptomycin was a "dead drug." (Tr. at 952, 1016 (Guglielmo); Tr. at 935–36 (Moellering).) If the consensus was that daptomycin was dead, it is not clear why there would be a need to develop a commercially viable purification process. Also taking into account the nexus problem, the court is not convinced by Cubist's long-felt but unmet need argument.

Cubist also argues that the propensity of daptomycin to form micelles was an unexpected, surprising property, first observed by the inventors of the purity patents. (Tr. at 913–14 (Myerson).) Cubist argues this surprising observation demonstrates that the asserted claims were non-obvious. Hospira does not appear to challenge Cubist's argument. Nonetheless, the court is not convinced this factor is entitled to serious weight. Cubist being the first to observe daptomycin's micelle-forming properties offers some objective evidence of non-obviousness, but the court has already explained that the Lakey reference taught that daptomycin behaved like a surfactant and formed aggregates under certain conditions. (DTX-345.) One skilled in the art would have recognized micelle-filtration as a possible means of purification. Thus, Cubist's unexpected results consideration is a rehash of a question the court has already decided. Being first to observe the property does not mean the property was non-obvious.

Finally, Hospira asserts Eli Lilly's ability to produce 98% pure daptomycin over a decade before the priority date of Cubist's purity patents weighs in favor of an obviousness finding. *See Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) ("Independently made, simultaneous inventions, made 'within a comparatively short space of time,' are persuasive evidence that the claimed apparatus 'was the product only of ordinary mechanical or engineering skill.'" (quoting *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184 (1925))). The clinical studies conducted by Eli Lilly (discussed in the previous section) used daptomycin batches with purity levels reaching upwards of 98%. (DTX-079.) The court agrees with Hospira that Eli Lilly's production of similarly pure daptomycin lots—not just simultaneous with, but considerably prior to Cubist's patented invention—is objective support for an obviousness determination.

Ultimately, the court finds that secondary considerations do not upset Hospira's *prima facie* showing that the asserted claims of the purity patents are obvious. Hospira has made this showing by clear and convincing evidence. The '238 and '342 Patents are invalid as obvious under § 103.

**3. Derivation**

Hospira finally argues that the purity patents are invalid because they were derived from sources other than the named inventors—in other words, the inventors identified on the purity patents did not in fact conceive of the claimed invention. Hospira argues the purity patents are therefore invalid under § 102(f).[14]

As Cubist identifies, however, Hospira's § 102(f) invalidity challenge is untimely. Although Hospira's pleadings asserted generally that all the asserted claims of the patents-in-suit were invalid under §§ 102 and 103 (D.I. 8), there were no other indications throughout the pretrial litigation that Hospira intended to raise a derivation defense. As required by the District of Delaware Local Rules, the parties submitted a joint proposed pretrial order, including the language: "This Order will control the course of the trial and may not be amended except by consent of the parties and the Court, or by order of the Court to prevent manifest injustice." (D.I. 109 at 11); *see* D. Del. LR 16.3(d)(4). Yet, nowhere in the parties' statement of contested facts or in Hospira's proposed findings of fact and conclusions of law is derivation or § 102(f) mentioned. As a result, Cubist was unfairly confronted with this invalidity challenge for the first time at trial. Moreover, § 282 provides notice procedures requiring that parties to patent lawsuits share certain information concerning patent validity—including prior inventorship arguments—with opposing counsel. 35 U.S.C. § 282. The Federal Circuit has stated:

[14] Section 102(f) stated: "A person shall be entitled to a patent unless . . . he did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f). The provision was eliminated by the America Invents Act ("AIA"), Pub. L. No. 112-29, § 3, 125 Stat. 284, 285–87 (2011), although proper inventorship remains a requirement of patentability through § 101.

> Recognizing the evolving nature of the contentions of the parties leading up to trial and to protect patentees from unfair and prejudicial surprise at trial, Congress established 35 U.S.C. § 282 to provide a statutory outer limit for the disclosure of certain information relating specifically to *defenses* to be relied upon by an accused infringer at trial.

*Woods v. DeAngelo Marine Exhaust, Inc.*, 692 F.3d 1272, 1280 (Fed. Cir. 2012) (emphasis in original); *see also ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 551 (Fed.Cir.1998) ("The purpose of § 282, like that of the Federal Rules, is to prevent unfair and prejudicial surprise . . . .").

The court finds that Hospira waived its derivation defense by failing to give notice of or assert it prior to trial.

## IV. CONCLUSION

For the reasons stated above, the court concludes that: (1) the Certificate of Correction issued for the RE'071 Patent is not invalid, and therefore Hospira's products infringe the RE'071 Patent; (2) the RE'071 Patent is not invalid for lack of written description; (3) the RE'071 Patent is not invalid for improper recapture; (4) a revision to the court's claim construction of the term "daptomycin" in the '967, '689, '238, and '342 Patents is not warranted, and therefore Hospira's products infringe the '967, '689, '238, and '342 Patents; (5) the '967, '689, '238, and '342 Patents are not invalid for lack of written description; (6) the asserted claims of the '967 Patent are invalid due to anticipation; (7) the asserted claims of the '967 and '689 Patents are invalid due to obviousness; (8) claim 98 of the '238 Patent is invalid as anticipated; (9) the asserted claims of the '238 and '342 Patents are invalid due to obviousness; (10) Hospira's § 102(f) derivation defense is untimely and precluded; and (11) each of the parties' Rule 52(c) motions are granted in part and denied in part.[15]

[15] As noted, all parties submitted Proposed Findings of Fact and Conclusions of Law, requesting that the court find in its favor on issues of obviousness, anticipation, indefiniteness, written description, and infringement. For the

Dated: December 8, 2014

UNITED STATES DISTRICT JUDGE

reasons stated above and based on the court's findings, the parties Rule 52(c) motions are granted in part and denied in part.