IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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| CUBIST PHARMACEUTICALS, INC., | ) | |
| | ) | |
| Plaintiff, | ) | |
| | ) | |
| v. | ) | C.A. No. 09-189 (GMS) |
| | ) | |
| TEVA PARENTERAL MEDICINES, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES LTD., | ) | |
| | ) | |
| Defendants. | ) | |

**CUBIST PHARMACEUTICALS, INC.'S**
**OPENING CLAIM CONSTRUCTION BRIEF**


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## I. INTRODUCTION

Cubist Pharmaceuticals, Inc. ("Cubist") filed this patent infringement action after receiving notice that defendants Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceuticals Industries Ltd. (collectively "Teva") intend to market a generic version of Cubicin® before expiration of Cubist's three Orange Book listed patents.[1] Cubicin®, which contains the antibacterial agent daptomycin, is approved for the treatment of serious and potentially fatal skin, bloodstream and heart infections caused by Gram-positive bacteria.

Two of the three asserted patents, U.S. Patent Nos. 6,468,967 ("the '967 patent") and 6,852,689 ("the '689 patent"), are related[2] and claim novel methods for administering daptomycin in an amount sufficient to treat serious bacterial infections while minimizing an adverse side effect known as "skeletal muscle toxicity." Although the parties have substantially narrowed the number of claim terms to be construed by the Court, two terms common to the '967 and '689 patents remain in dispute: "a therapeutically effective amount of daptomycin" and "at a dosage interval that minimizes skeletal muscle toxicity."

The third patent, U.S. Patent No. RE39,071 ("RE'071"), claims a highly purified composition of daptomycin containing only small amounts of two daptomycin-related impurities. One term in the RE'071 patent requires construction by the Court: "in substantially pure form."

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1 This action is brought pursuant to the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (the "Hatch-Waxman Act").

2 The '689 patent is a continuation of the '967 patent under 35 U.S.C. §120. The two patents share a common specification.

## II. THE CUBIST PATENTS

### A. The '967 and '689 Inventors Discovered How to Administer Effective Amounts of Daptomycin While Minimizing Skeletal Muscle Toxicity

In the late 1970s, researchers at Eli Lilly and Co. ("Lilly") discovered daptomycin[3] and subsequently found that it was effective in treating some bacterial infections. '967 patent, col. 1, l. 63 – col. 2, l. 2 (J.A. at A8); '967 File History, Tally Decl. at 3 (J.A. at A133). Lilly clinical studies showed, however, that doses of daptomycin sufficient to treat more serious infections could be toxic to patients' skeletal muscle and cause adverse side effects such as muscular weakness and pain. '967 patent, col. 1, l. 63 – col. 2, l. 17 (J.A. at A8). Unable to identify a dosing regimen that was both safe and effective to treat serious bacterial infections, Lilly discontinued its daptomycin clinical studies in the early 1990s. '967 patent, col. 2, ll. 17 – 20 (J.A. at A8). The need for new therapies nevertheless grew due to the widespread proliferation of Gram-positive bacterial infections,[4] including infections resistant to existing treatments. '967 patent, col. 1:21 – 23 (J.A. at A8). Thus, at the time of the inventions claimed in Cubist's '967 and '689 patents, a significant but unmet need existed for a method to administer daptomycin in amounts sufficient to treat serious bacterial infections, while minimizing the adverse side effect of skeletal muscle toxicity. '967 patent, col. 2, ll. 40 – 43 (J.A. at A8).

Against this backdrop, Cubist licensed daptomycin from Lilly and sought to develop the product. During the course of their research, scientists at Cubist made a surprising observation: skeletal muscle toxicity correlated to the *interval between daptomycin doses* and not just to the

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[3] Daptomycin is produced by a bacterium known as *streptomyces roseosporus.* '967 patent, col. 1:41 – 43 (Joint Appendix ("J.A.") at A8).

[4] Many bacteria that cause serious diseases in humans are Gram-positive, a term that refers to organisms that are stained dark blue or violet during a classification process known as Gram staining. This is in contrast to Gram-negative bacteria, which cannot retain a crystal violet stain. '967 patent, col. 1, ll. 21 – 36 (J.A. at A8).

magnitude of the dose. '967 patent, col. 4, ll. 22 – 23, 37 – 42, and 46 – 48 (J.A. at A9). For example, studies in dogs showed that daptomycin administered in 25 mg/kg doses three times a day (for a total daily dose of 75 mg/kg) over 20 days unexpectedly caused higher muscle toxicity than administration of 75 mg/kg doses every 24 hours over 20 days. '967 patent, col. 4, ll. 21 – 36 (J.A. at A9); *id.* col. 9, ll. 28 – 52 (J.A. at A12); *id.* Table 2 (J.A. at A12); *id.* figs. 1A, 1B (J.A. at A5). Human clinical studies confirmed the results of the dog studies. '967 patent, col. 4, l. 64 – col. 5, l. 13 (J.A. at A9-10). Thus, the inventors discovered that daptomycin could treat serious infections safely (*i.e.*, with minimal toxicity) if administered no more than once a day. '967 patent, col. 4, ll. 60 – 63 (J.A. at A9).

Based on this discovery, the two method patents at issue—the '967 and '689 patents—teach and claim methods for administering a therapeutically effective amount of daptomycin using dosing regimens that minimize skeletal muscle toxicity. For example, claim 1 of the '967 patent recites:

> A method 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 3 to 75 mg/kg of daptomycin **at a dosage interval that minimizes skeletal muscle toxicity**, wherein the daptomycin dose is repeatedly administered at a dosage interval of once every 24 hours to once every 48 hours.

(J.A. at A14) (emphasis added). The asserted claims of the '967 and '689 patents,[5] including those that depend from claim 1 of the '967 patent further limit the dose and dosage interval. Claim 26 of the '967 patent, from which asserted claims 27, 28, 34, 35, 44, and 45 depend, recites a "method for treating or eradicating a bacterial infection" and adds the limitation "until said bacterial infection is treated or eradicated." (J.A. at A15.)

[5] Cubist asserts infringement of claims 3, 4, 5, 16, 17, 27, 28, 34, 35, 42, 43, 44, and 45 of the '967 patent and claims 48, 49, 50, 51, and 52 of the '689 patent.

### B. The RE'071 Inventors Discovered Daptomycin With Limited Amounts of Two Impurities

Daptomycin, originally designated by Lilly as "LY146032," is a natural product produced by a living organism, the bacterium known as *Streptomyces roseosporus*. '967 patent, col. 1, ll. 41 - 43 (J.A. at A8). Daptomycin is produced (along with numerous other substances) by the fermentation of *Streptomyces roseosporus*. *Id.* The inventors of the RE'071 patent discovered that the fermentation mixture containing daptomycin also contained two impurities that are generated as daptomycin degrades. These impurities, designated "anhydro-LY146032" and "isomer-LY146032," form when daptomycin undergoes a chemical reaction known as "aspartyl transpeptidation."[6] RE'071, cols. 7, l. 61 – 8, l. 25 (J.A. at A40). The inventors also discovered that the two impurities are more prevalent when the pH of a daptomycin solution is between 4 and 6 during the isolation process. *Id.* In identifying how the two degradation products are formed, the inventors also discovered that the degradation products can be minimized and separated from the parent compound to create a more pure form of daptomycin than was previously available. RE'071, col. 7, ll. 61 – 65 (J.A. at 40); *id.* col. 8, ll. 45 – 49 (J.A. at A40); *id.* Examples 1-5 (J.A. at A42-43). Thus, the RE'071 patent is directed to, among other things, compositions of daptomycin with limited amounts of anhydro-LY146032 and isomer-LY146032.[7]

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[6] The two impurities are derived from daptomycin and, consequently, have closely related chemical structures. RE'071, col. 7, ll. 62 – 67 (J.A. at A40); '226 File History, Debono Decl., at 2-3 (J.A. at A401-02).

[7] Cubist asserts infringement of claims 18-20, 26, and 28 of the RE'071 patent. The RE'071 patent reissued from U.S. Patent No. 5,912,226. Applicants sought the reissue to claim combinations of daptomycin, anhydro-LY146032, and isomer-LY146032, where the combination contained less than 6% or less than 2.5% of anhydro-LY146032 and isomer-LY146032. RE'071 File History, Application, at 4-5 (J.A. at 323-24).

## III. ARGUMENT

### A. Claim Construction Principles

In *Phillips v. AWH Corp.*, the Federal Circuit explained that claim terms should be interpreted in the context of a patent's "intrinsic evidence," including the (1) claim language, (2) the specification, and (3) the prosecution history. 415 F.3d 1303, 1312-1314 (Fed. Cir. 2005); *see also Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005) ("We cannot look at the ordinary meaning of the term . . . in a vacuum. Rather, we must look at the ordinary meaning in the context of the written description and the prosecution history.") (citation omitted).

*Phillips* also reaffirmed that "the words of a claim 'are generally given their ordinary and customary meaning.'" 415 F.3d at 1312 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996), and citing *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999); *Renishaw PLC v. Marposs Societa per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998)). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Renishaw PLC*, 158 F.3d at 1313. The context in which a term is used in an asserted claim also can be "highly instructive." *Id.* at 1249.

In addition, "the specification 'is always highly relevant to the claim construction analysis'" and is considered the "'single best guide to the meaning of a disputed term.'" *Phillips*, 415 F.3d at 1315 (quoting *Vitronics Corp.*, 90 F.3d at 1582). Indeed, the patentee can use the specification to ascribe special meaning to otherwise ordinary terms. *See id*. at 1316 ("our cases recognize that the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess").

A patent's prosecution history can also be useful in defining claim terms. *See Phillips*, 415 F.3d at 1317 ("Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent."). Statements made during prosecution illustrate what the patentee understood to be the scope of the invention. *See Bd. of Regents of the Univ. of Texas Sys. v. BENQ Am. Corp.*, 533 F.3d 1362, 1369-70 (Fed. Cir. 2008).

### B. The Disputed Claim Terms in the '967 and '689 Patents Are Limitations And Should Be Construed As Proposed By Cubist

The parties dispute two terms in the claims of the '967 and '689 patents: (1) "a therapeutically effective amount of daptomycin," and (2) "at a dosage interval that minimizes skeletal muscle toxicity." Cubist proposes construing these limitations in a manner consistent with their plain language, the written description of the claimed invention in the specification, and the file history. Teva, by contrast, denies that they are limitations at all, even though they are plainly important to the invention claimed; indeed, the Patent Office described one of them as an "essential element" of the invention.

#### *1. "a therapeutically effective amount of daptomycin" means "an amount of daptomycin that is efficacious in reducing or eliminating the Gram-positive bacterial infection"*

| Cubist's Proposed Construction | Teva's Proposed Construction |
|---|---|
| "An amount of daptomycin that is efficacious in reducing or eliminating the Gram-positive bacterial infection." | Non-limiting as merely statement of intended result of specific dose limitation. |

The term "a therapeutically effective amount of daptomycin" should be construed as "an amount of daptomycin that is efficacious in reducing or eliminating a Gram-positive bacterial

infection."[8] The administration of an amount of daptomycin sufficient to treat bacterial infection is a central aspect of the claimed invention. The claim term "therapeutically effective amount" therefore encompasses the *total amount* of daptomycin (administered in multiple, successive doses) effective to reduce or eliminate an infection. Thus, contrary to Teva's suggestion, the term "therapeutically effective amount" is not redundant of the recited dose limitation, but constitutes a separate (and important) limitation of the claimed invention.

The claims separately recite a "therapeutically effective amount" of daptomycin and a "dose" of daptomycin. For example, claim 1 of the '967 patent clearly differentiates between "amount" and "dose" insofar as it claims a *method* of administering a "therapeutically effective amount" of daptomycin in a specific "dose" at a specific "dosage interval." '967 patent, cl. 1. (J.A. at A14). Different terms within the body of a claim presumptively have their own meaning, such that "therapeutically effective amount" must have a different meaning from "dose." *See, e.g., Bancorp Servs., L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1373 (Fed. Cir. 2004) ("[T]he use of both terms in close proximity in the same claim gives rise to an inference that a different meaning should be assigned to each."); *TDM Am., LLC v. United States*, 85 Fed. Cl. 774, 801 (2009) ("[T]he Court infers that different words within a claim have different meanings."). The same conclusion follows from the structure of the claim, which indicates that the claimed dose must be administered "repeatedly," thereby making clear that the "therapeutically effective amount" consists of more than a single dose.

[8] The term "therapeutically effective amount" appears in the '967 patent in claim 1, on which asserted claims 3, 4, and 5 depend; claim 12, on which asserted claims 16, 17, 42, and 43 depend; and claim 26, on which asserted claims 27, 28, 34, 35, 44, and 45 depend. The term appears in the '689 patent in claim 47, on which asserted claims 48, 49, 50, 51, and 52 depend.

Teva's suggestion that the term "therapeutically effective amount" is non-limiting because it is the same as the claimed individual "dose limitation" is inconsistent with the caselaw, as well as language of the claims, the specification, and the file history. Indeed, the Federal Circuit disfavors constructions that "ascribe[] no meaning to the term . . . not already implicit in the rest of the claim." *Mangosoft, Inc. v. Oracle Corp.*, 525 F.3d 1327, 1330-31 (Fed. Cir. 2008); *see also Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1377-78 (Fed. Cir. 2009) (finding that construction of a claim that reads a word out of the claim, rendering the word in the claim "superfluous," to be in error); *Merck & Co. v. Teva Pharms, USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so.").

The common specification also demonstrates that, far from being non-limiting, administration of a therapeutically effective amount of daptomycin is a central characteristic of the claimed invention: "[t]he methods of the present invention comprise administering daptomycin … to a patient in need thereof *an amount that is efficacious in reducing or eliminating the gram-positive bacterial infection*…." '967 patent, col. 7, ll. 17 – 24 (J.A. at A11) (emphasis added); *see also id.* Abstract (J.A. at A2) ("The invention provides methods for administering a therapeutically effective amount of daptomycin while minimizing skeletal muscle toxicity."). The requirement of the claim that the total amount of daptomycin administered be "therapeutically effective" is essential to solving the problem addressed by the claimed invention, namely the "great need to develop methods for administration of *effective amounts* of daptomycin that will also minimize adverse skeletal muscle effects." '967 patent, col. 2, ll. 40 – 43 (J.A. at A2). For the claimed method to cover the administration of a "therapeutically effective amount," this important term must be given meaning.

Other parts of the specification provide additional support for Cubist's proposed construction. For example, the dosing regimens described in the specification require administration of daptomycin for at least two days and for as long as three months. *See*, *e.g.*, '967 patent, col. 6, ll. 31 – 35 (J.A. at A10); col. 15, ll. 55 – 61 (J.A. at A15); col. 16, ll. 42 – 52 (J.A. at A15); *see also* '967 patent col. 6, ll. 29 – 30 (J.A. at A10) ("Daptomycin may be administered according to this method until the bacterial infection is eradicated or reduced."). This further demonstrates that the "therapeutically effective amount" required to reduce or eliminate infection consists of multiple doses and is therefore not redundant of the separate "dose" limitation.

Once the term "therapeutically effective amount" is found to be limiting, the correct construction is plain from the language of the claims, as well as the specification. The "therapeutically effective amount" includes the total amount of daptomycin administered in multiple successive doses in order to reduce or eliminate the gram-positive bacterial infection. '967 patent, cl. 1 (J.A. at A14); *id.* col. 7, ll. 17 – 24 (J.A. at A11); *id.* Abstract (J.A. at A2). Indeed, the specification identifies criteria for determining when a dosing regimen is efficacious. *See* '967 patent, col. 14, ll. 11 – 21 (J.A. at A14). Accordingly, the term "therapeutically effective amount" limits the claims in which it appears to methods of administration of an overall amount of daptomycin that is efficacious in reducing or eliminating the infection when administered using the specified dose and dosing interval.

*2. "at a dosage interval that minimizes skeletal muscle toxicity" means "at a dosage interval that reduces skeletal muscle toxicity in comparison to dosing more than once every 24 hours"*

| Cubist's Proposed Construction | Teva's Proposed Construction |
|---|---|
| "At a dosage interval that reduces skeletal muscle toxicity in comparison to dosing more than once every 24 hours." | Non-limiting as merely statement of intended result of specific dosage interval claimed. |

The term "at a dosage interval that minimizes skeletal muscle toxicity" is a limitation and means "at a dosage interval that reduces skeletal muscle toxicity in comparison to dosing more than once every 24 hours.[9]

Teva's argument that this claim language has no meaning and can simply be ignored is contrary to established claim construction principles. *See Agilent Techs.*, 567 F.3d at 1377-78; *Merck & Co.*, 395 F.3d at 1372; *Mangosoft, Inc.*, 525 F.3d at 1330-31. Teva's position also contradicts the intrinsic evidence, including the Examiner's insistence that the reduction of skeletal muscle toxicity was an "essential element" of the invention. Indeed, the Examiner required that the element of reducing skeletal muscle toxicity be added to every claim of both applications before allowing the patents to issue. To construe the term as non-limiting would eviscerate a fundamental element of the invention as interpreted by both the Applicants and the Patent Office.

During prosecution of the '967 patent, the Examiner rejected proposed claims 32 and 33 under 35 U.S.C. § 112, second paragraph, stating, "[i]n the Specification, it appears that an *essential element of the invention is that it does not cause muscle toxicity*, however, Claims 32, 33 do not appear to have this limitation in the claims." '967 File History, April 11, 2000 First

[9] The term "at a dosage interval that minimizes skeletal muscle toxicity" appears in the '967 patent in claim 1, from which asserted claims 3, 4, and 5 depend; claim 12, from which asserted claims 16, 17, 42, and 43 depend; and claim 26, from which asserted claims 27, 28, 34, 35, 44, and 45 depend. The term appears in the '689 patent in claim 47, from which asserted claims 48, 49, 50, 51, and 52 depend.

Office Action, at 3 (J.A. at A103)(emphasis added). In response, Applicants amended the body of claim 32 to include a limitation regarding skeletal muscle toxicity and amended the *preamble* of claim 6 to recite "A method for administering daptomycin at a dosage interval that does not result in skeletal muscle toxicity, comprising ...." '967 File History, September 11, 2000 Response, at 2-4 (J.A. at A110-12).[10]

In a subsequent Office Action, the Examiner rejected another claim – claim 16 – under 35 U.S.C. § 112, second paragraph, stating, "[i]n the Specification, it appears that a[n] *essential element of the invention is that it does not cause muscle toxicity*, however, Claim 16 do[es] not appear to have this limitation in the claim." '967 File History, Second Office Action, at 2 (J.A. at A142)(emphasis added). The Examiner's Interview Summary after a May 1, 2001 interview states that "Examiner suggested amending claims to state *minimization of toxicity in body of claims* …." '967 File History, Interview Summary, at 1 (J.A. at A148) (emphasis added). Applicants then filed a response, amending (i) the body of claim 16 to recite "at a dosage interval that minimizes skeletal muscle toxicity," and (ii) claim 6 to move the skeletal muscle toxicity limitation from the preamble to the body of the claim, and to change "at a dosage interval that does not result in skeletal muscle toxicity" to "at a dosage interval that minimizes skeletal muscle toxicity." '967 File History, June 4, 2001 Response, at 2, 4, (J.A. at A151; A153); *id.* listing of Amended and Added Claims (J.A. at A161-64). The Examiner then issued a Notice of Allowance stating:

> The present invention is directed to a method of administering daptomycin … at a dosage interval that *minimizes muscle toxicity*, wherein the daptomycin dose is repeatedly administered at a dosage interval of once every 24 hours to once every 48 hours.

[10] Claim 33 was canceled for reasons not relevant here.

> … the claimed invention, as amended, is not expressly disclosed by the prior art and it is unexpected that repeatedly administering at dosage intervals of once every 24 hours to once every 48 hours will *minimize muscle toxicity* ...

'967 File History, August 13, 2001 Notice of Allowance, at 2 (J.A. at A167) (emphasis added).

Thus, the file history of the '967 patent clearly shows that (1) the Examiner considered minimization of skeletal muscle toxicity to be an essential element of the claims, required for their patentability; (2) at the Examiner's direction, Applicants amended several independent claims to include this limitation, and to place the element regarding reducing muscle toxicity into the body of the claim, rather than in the preamble; and (3) allowance was based on minimization of muscle toxicity as a fundamental element of the invention.

The '689 patent's file history reveals that the Examiner similarly viewed the element of reducing skeletal muscle toxicity as critical to the invention. In a First Office Action, the Examiner rejected proposed claims 6 – 15 and 26 under 35 U.S.C. § 112, second paragraph, stating, "[i]n the Specification, it appears that a[n] *essential element of the invention is that it does not cause muscle toxicity*, however, Claims 6 – 10, 12 – 15 do not appear to have this limitation in the claims and claims 11 and 26 do not require that the claims contain said limitations." '689 File History, May 21, 2002 First Office Action, at 4 (J.A. at A174) (emphasis added). As in the prosecution of the '967 patent, Applicants overcame the rejection by amending claim 1 to recite "at a dosage interval that minimizes skeletal muscle toxicity," canceled claim 6, and amended the remaining claims to depend from claim 1. '689 File History, November 20, 2002 Response, at 3 (J.A. at A184) and Marked-Up Version of Amended Claims (J.A. at A199).

In addition, during prosecution of both patents, the Applicants repeatedly distinguished the prior art cited by the Examiner on the grounds that it did not acknowledge (let alone solve) the problem of avoiding skeletal muscle toxicity. For example, in distinguishing prior art cited

by the Examiner during prosecution of the '967 patent, Applicants stated: "None of the '226, Woodworth, Watanakunakorn, Thibault or Leclercq, either alone or taken together, teach or suggest administration of daptomycin at a dosage interval *that minimizes skeletal muscle toxicity*." *See* '967 File History, June 4, 2001 Response to Office Action, at 9 (J.A. at A158) (emphasis added). Applicants again relied on this important aspect of the invention to distinguish prior art cited during prosecution of the '689 patent, stating: "Pyrka, Kennedy and Van Der Auwera do not provide any teaching or suggestion of how to design an efficacious dosing protocol that *avoids skeletal muscle toxicity*." '689 File History, November 20, 2002 Response to Office Action, at 12 (J.A. at A193) (emphasis added).

In similar circumstances, the Federal Circuit has found claim language to be limiting. For example, the Federal Circuit found that even language in a *preamble* is limiting where the Examiner finds it essential to patentability. *Cf. Invitrogen Corp. v. Biocrest Mfg. L.P.*, 327 F.3d 1364, 1370 (Fed. Cir. 2003) (noting that a claim preamble acts as a limitation where the patent examiner found it to be essential to the invention) (citing cases). Similarly, the Federal Circuit very recently found a claim term contained in a preamble to be limiting where "the patentee has relied on it during prosecution to distinguish prior art, as such reliance demonstrates that the feature disclosed in the preamble is necessary to the patentability of the claim." *Hearing Components, Inc. v. Shure Inc.*, No. 09-1364, Slip Op. at 11 (Fed. Cir. April 1, 2010). That reasoning applies *a fortiori* to the "minimizing skeletal muscle toxicity" limitation, which the Examiner directed Applicants to add to the *body* of the claims and the Applicants repeatedly discussed as a distinguishing factor over the prior art.

In addition to mirroring the plain language of the claim and the prosecution history, Cubist's construction is supported by the specification, which states:

> The present invention addresses the problem of skeletal muscle toxicity of high doses of lipopeptide antibiotics such as daptomycin[.]

'967 patent, col. 3, ll. 14 – 16 (J.A. at A9). The "Summary of Invention" repeatedly references minimizing skeletal muscle toxicity as an element of the claimed invention. *See, e.g.*, '967 patent, col. 3, ll. 24 – 27 (J.A. at A9); *id.* col. 5, ll. 40 – 50 (J.A. at A10); *id.* col. 6, ll. 46-50 (J.A. at A10); *id.* col. 7, ll. 17 – 23 (J.A. at A11). Like the claimed "therapeutically effective amount of daptomycin," the limitation regarding minimizing skeletal muscle toxicity is consistent with—and indeed, essential to—solving the "great need to develop methods for administration of effective amounts of daptomycin *that will also minimize adverse skeletal muscle effects*." '967 patent, col. 2, ll. 40 – 43 (J.A. at A8)(emphasis added).

Once the "minimizing skeletal muscle toxicity" term is found to be limiting, the correct construction is clear. The specification makes plain that the present invention provides methods for administering daptomycin that minimize skeletal muscle toxicity compared to prior methods for administering daptomycin. '967 patent, col. 5, ll. 41 – 44 (J.A. at A10); *see also id*. col. 7, ll. 17 – 23 (J.A. at A11). Those prior methods included administering daptomycin more frequently than once every 24 hours. Indeed, the data and examples included in the patent focus on comparing the claimed dosing regimens with prior art dosing regimens that administered daptomycin more than once a day. *See, e.g.*, '967 patent col. 2, ll. 4 – 20 (J.A. at A8); *id.* col. 4, ll. 22 – 28 (J.A. at A9); *id.* col. 5, ll. 18 – 22 (J.A. at A10); *id.* col. 10, ll. 17 – 40 (J.A. at A12); *id.* col. 10, ll. 56 – 59 (J.A. at A12); *id.* col. 10, ll. 64 – 67 (J.A. at A12); *id.* col. 11, ll. 26 – 32 (J.A. at A13); *id.* col. 12, ll. 1 – 15 (J.A. at A13). For example, the specification compares the claimed dosing regimen with prior art regimens in which daptomycin was administered twice or three times a day (*see, e.g., id.* col. 2, ll. 4 – 20 (J.A. at A8)), resulting in the toxicity that led to Lilly's discontinuation of clinical trials. Similarly, the examples describe Cubist studies

demonstrating that dosing no more than once every 24 hours reduces muscle toxicity compared to dosing more frequently. *See, e.g.*, *id.* col. 4, ll. 22 – 33 (J.A. at A9); *id.* col. 5, ll. 18 – 22 (J.A. at A10); *id.* col. 10, ll. 17 – 52 (J.A. at A12); *id.* col. 10, ll. 56 – 59 (J.A. at A12); *id.* col. 10, ll. 64 – 67 (J.A. at A12).

Cubist's construction is also supported by the language of original claim 23 in the application that led to the '967 patent, which recited: "[t]he method according to claim 16, wherein said method reduces muscle toxicity compared to administration of daptomycin at a more frequent interval than 24 hours." '967 File History, Application No. 09/406,568, at 29 (J.A. at A90). During the May 1, 2001 interview, the Examiner "suggested amending claims to state *minimization of toxicity in body of claims* …." '967 File History, Interview Summary, at 1 (J.A. at A148)(emphasis added). After claim 16 was amended to recite "at a dosage interval that minimizes skeletal muscle toxicity," claim 23 was canceled because amended claim 16 made it redundant. *See* '967 File History, June 4, 2001 Response, at 3, 4, 8 (J.A. at A152-53, A157); *id.* listing of Amended and Added Claims (J.A. at A161-64). Accordingly, the claim term "at a dosage interval that minimizes skeletal muscle toxicity" refers to reducing toxicity compared to administration more than once every 24 hours.

Thus, the claim term is properly construed as "at a dosage interval that reduces skeletal muscle toxicity in comparison to dosing more than once every 24 hours."

### C. Cubist's Proposed Construction of "In Substantially Pure Form" in The RE'071 Patent Is Consistent with the Claims and the Specification

| Cubist's Proposed Construction | Teva's Proposed Construction |
|---|---|
| "Wherein the formula 3 compound is LY146032 and the combination contains less than 2.5% of a combined total of the formula 1 compound (*i.e.*, anhydro-LY146032) and the formula 2 compound (*i.e.*, isomer-LY146032)." | "Wherein the formula 3 compound is LY146032 which contains less than 2.5 percent of a combined total of anhydro-LY146032 and isomer-LY146032." |

The parties disagree as to one term in Claim 20 of the RE'071 patent -- "in substantially pure form." That term should be construed as "wherein the formula 3 compound is LY146032 and the combination contains less than 2.5% of a combined total of the formula 1 compound (*i.e.*, anhydro-LY146032) and the formula 2 compound (*i.e.*, isomer-LY146032)." Cubist's proposed construction is consistent with the language and structure of Claim 20 and the other independent claims, as well as the explicit definition of "in substantially pure form" in the specification.

Claim 20 is complicated by its illustrations of three separate chemical formulas, which it calls "the formula 1 compound," "the formula 2 compound," and "the formula 3 compound." The parties appear to agree on what the three formulas actually represent. The formula 1 compound is an impurity, or degradation product, designated as "anhydro-LY146032." RE'071 patent, col. 8, ll. 7 – 10 (J.A. at A40). The formula 2 compound is a second impurity or degradation product designated as "isomer-LY146032." RE'071 patent, col. 8, ll. 11 – 15 (J.A. at A40). And the formula 3 compound is daptomycin itself, which is designated LY146032. RE'071 patent, col. 7, ll. 1-27; ll. 56 – 60 (J.A. at A40).

Claim 20 recites a simple composition comprising a combination of the three compounds in which the two impurities make up less than 2.5 percent of the combination. An accurate but

simplified version of Claim 20—replacing the chemical formulas with shorthand descriptions—would read:

> An antibiotic composition useful for the treatment of bacterial infections comprising a combination of a compound of formula 1 [*i.e.*, anhydro-LY146032], a compound of formula 2 [*i.e.*, isomer-LY146032] and a compound of formula 3 [*i.e.*, an effective antibacterial amount of LY146032)] … in substantially pure form.

The parties disagree only as to the meaning of "in substantially pure form." Cubist's proposed construction tracks the language of the claim, namely that the amounts of the two impurities are defined with respect to the "*combination*" of the three compounds. The other independent claims support this construction because they recite compositions or formulations including a combination of a compound of formula 1 (anhydro-LY146032), a compound of formula 2 (isomer-LY146032) and a compound of formula 3 (LY146032), wherein "the total amount of the compound of formula 1 and the compound of formula 2 … *in the combination* is less than 6 weight percent." RE'071 Patent, cls. 18, 26, 30 (J.A. at A44) (emphasis added). Thus, the claimed invention clearly defines the percentage of the two impurities relative to the *combination* of LY146032, anhydro-LY146032 and isomer-LY146032. "In substantially pure form" in claim 20 is simply a shorthand for stating that the combination contains less than 2.5% of the two impurities. The specification explicitly defines "in substantially pure form," stating as follows:

> The term "in substantially pure form" refers to LY146032 which contains less than 2.5 percent of a combined total of anhydro-LY146032 and isomer-LY146032.

RE'071 patent, col. 8, ll. 55 – 57 (J.A. at A40).

The prosecution history of RE'071 also supports Cubist's proposed construction. For example, in a December 21, 2000 Amendment and Response to Office Action, the Applicants explained that "this weight percent recited in the claims (and in the '226 Patent) is based on *a*

*total of the three compounds (i.e. formula 1, formula 2 and formula 3 compounds)* or salts thereof …. It is within this combination that the combined total of the formula 1 and formula 2 compounds (or salts) is less than or equal to 2.5 weight percent…." RE'071 File History, December 21, 2000 Amendment and Response, at 17 (J.A. at A281)(emphasis added). And in a July 3, 2002 Amendment and Response, Applicants defined "substantially pure form" as "containing less than 2.5 weight percent of a combined total of anhydro- and isomer- compounds (or salts)." RE'071 File History, July 3, 2002 Amendment and Response, at 15 (J.A. at A316). Accordingly, the term "in substantially pure form" means that the combination in claim 20 contains less than 2.5 percent of the two impurities (anhydro-LY146032 and isomer-LY146032).

Teva's proposed construction differs from Cubist's construction only in one respect: Teva suggests that *the formula 3 compound*, as opposed to the combination of the three compounds, contains less than 2.5 percent of the formula 1 and formula 2 compounds (*i.e.*, anhydro-LY146032 and isomer-LY146032). That construction is untenable, because Claim 20 defines the formula 1, 2, and 3 compounds separately, using a different chemical formula for each. The formula 3 compound (as defined in Claim 20) does not contain *any* of the two impurities, *i.e.*, the formula 1 and formula 2 compounds. Rather, it is the *combination* of the three compounds (daptomycin/LY146032, anhydro-LY146032 and isomer-LY146032) that contains less than 2.5% of the two impurities.

## IV. CONCLUSION

For the foregoing reasons, Cubist requests that the Court construe the claims in the manner set forth in Cubist's proposed claim constructions.

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April 9, 2010

**CERTIFICATE OF SERVICE**

I hereby certify that April 9, 2010, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to:

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I further certify that I caused copies of the foregoing document to be served on April 9, 2010, upon the following in the manner indicated:

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