United States Court of Appeals for the Federal Circuit

CUBIST PHARMACEUTICALS, INC.,
Plaintiff-Cross-Appellant

v.

HOSPIRA, INC.,
Defendant-Appellant

2015-1197, 2015-1204, 2015-1259

Appeals from the United States District Court for the District of Delaware in No. 1:12-cv-00367-GMS, Judge Gregory M. Sleet.

Decided: November 12, 2015

WILLIAM F. LEE, Wilmer Cutler Pickering Hale and Dorr LLP, Boston, MA, argued for plaintiff-cross-appellant. Also represented by MARK CHRISTOPHER FLEMING, LISA JON PIROZZOLO; WILLIAM G. MCELWAIN, Washington, DC.

JAMES F. HURST, Kirkland & Ellis LLP, Chicago, IL, argued for defendant-appellant. Also represented by JOHN C. O'QUINN, Washington, DC; LESLIE M. SCHMIDT, New York, NY; STEFFEN NATHANAEL JOHNSON, JOVIAL WONG, Winston & Strawn LLP, Washington, DC; JAMES MATTHEW HILMERT, TYLER JOHANNES, GEORGE C.

LOMBARDI, Chicago, IL; STEPHEN R. SMEREK, Los Angeles, CA.

Before WALLACH, BRYSON, and HUGHES, *Circuit Judges.*

BRYSON, *Circuit Judge.*

This case arises under the Hatch-Waxman Act, which governs certain patent disputes between pharmaceutical companies.[1] The plaintiff, Cubist Pharmaceuticals, Inc., owns five patents that relate to the antibiotic daptomycin. The defendant, Hospira, Inc., sought authorization to sell a generic version of Cubist's daptomycin product, which led Cubist to file this action charging Hospira with patent infringement.

Daptomycin was developed by Eli Lilly & Co. ("Lilly"). The original patent to daptomycin expired in 2002. The five patents at issue in this case are all follow-on patents owned by Cubist. The first is U.S. Patent No. RE39,071 ("the '071 patent"), which is a reissue of U.S. Patent No. 5,912,226 ("the '226 patent") and is directed to antibiotic compounds, compositions, formulations, and methods of treating bacterial infections. The next two are U.S. Patent Nos. 6,852,689 and 6,468,967 ("the '689 and '967 patents"), which are entitled "Methods for Administration of Antibiotics" and are directed to dosage regimens for administering daptomycin. The final two are U.S. Patent Nos. 8,058,238 and 8,129,342 ("the '238 and '342 patents"), which are entitled "High Purity Lipopeptides" and

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[1] The Hatch-Waxman Act is the name commonly used to refer to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, the principal provisions of which are codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156 and 271(e)(2).

are directed to the purification of daptomycin compositions.

Cubist sells its daptomycin formulation under the trade name Cubicin. In 2011, Hospira filed an Abbreviated New Drug Application with the Food and Drug Administration seeking approval to manufacture and sell an equivalent daptomycin product prior to the expiration of Cubist's patents. Pursuant to procedures set forth in the Hatch-Waxman Act, Cubist then filed an action in the United States District Court for the District of Delaware, alleging that Hospira had infringed all five of Cubist's patents. Hospira responded by challenging the validity of the asserted claims of each of those patents. Two other related actions brought by Cubist were subsequently consolidated with the initial lawsuit.

Following a bench trial, the district court held some of the asserted claims of four of Cubist's patents invalid for anticipation and all the asserted claims of those patents invalid for obviousness. As for the fifth patent, the court held the two asserted claims not invalid and ruled that Hospira's proposed products infringed those claims. Both parties appeal from the portions of the judgment adverse to them. We affirm the judgment of the district court, relying heavily on the factual findings made by the court following the trial.

I

Hospira appeals from the district court's ruling that Hospira infringed claims 18 and 26 of the '071 patent and that those claims are not invalid. Hospira's appeal focuses on a certificate of correction granted to Cubist with regard to the '071 patent. The certificate corrected a diagram of the chemical structure of a compound described in the specification and recited in four of the claims of the '071 patent, including claims 18 and 26.

A

1

The asserted claims of the '071 patent recite an antibiotic composition and a pharmaceutical formulation, each comprising a combination of three compounds. The first and second compounds in each claim are daptomycin-related substances. The first is known as anhydrodaptomycin and the second is known as the beta isomer of daptomycin. The third compound, referred to as Formula 3, is the compound known in the art as daptomycin.[2]

The specification of the '071 patent describes the Formula 3 compound in three ways. First, it refers to the compound as "an A-21978C cyclic peptide." According to the specification, A-21978C cyclic peptides "are prepared from the A-21978C antibiotics," which are "a group of closely related, acidic peptide antibiotics" that are described in U.S. Patent No. 4,208,403 ("the '403 patent"). '071 patent, col. 6, ll. 59-61; col. 7, ll. 41-42. The '403 patent in turn describes the A-21978C antibiotics as being produced by a process involving the fermentation of the bacterium *Streptomyces roseosporus*.

Second, the specification of the '071 patent refers to the Formula 3 compound by the code name LY146032. That code name was assigned to the compound by Lilly and was known in the art to refer to daptomycin.

Third, the specification states that the Formula 3 compound has the following structure, where R^N is n-decanoyl:

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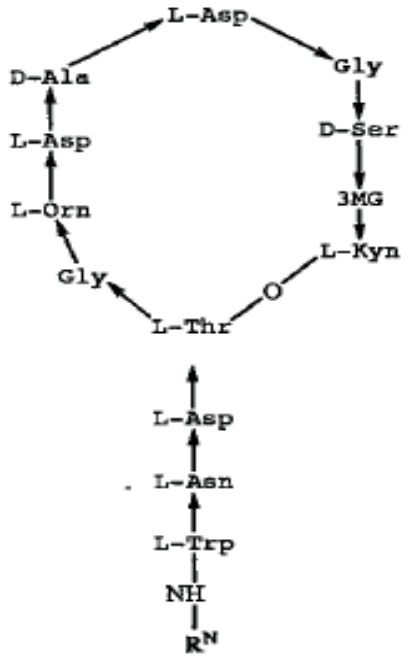
[2] For clarity, we refer to "daptomycin" as the compound that is found in Cubicin and was the subject of Hospira's Abbreviated New Drug Application.



It turns out that the structural diagram of the compound identified as Formula 3 and depicting daptomycin was inaccurate in one respect. The structure in the diagram contained 13 amino acids, including asparagine (abbreviated "Asn"). While the diagram accurately identified the amino acids and their location in the daptomycin molecule, it mistakenly identified the stereoisomer of the asparagine amino acid as the "L" stereoisomer of asparagine, rather than the "D" stereoisomer.

At the time the application for the '226 patent was filed, and until well after that patent was issued, it was universally believed that the asparagine amino acid in daptomycin was the L-isomer of asparagine, as set forth in the structural diagram. Years after the issuance of the '226 patent and after the reissue application for the '071 patent was filed, Lilly researchers discovered that daptomycin actually contains the D-isomer of asparagine, not the L-isomer.

In 2007, Cubist sought to correct the error by requesting a certificate of correction from the Patent and Trademark Office ("PTO") pursuant to 35 U.S.C. § 255. Cubist explained that the mistake in the patent as to the identity of the stereoisomer of asparagine was "the result of the mischaracterization of one of the A-21978C factors described by Formula 3." Specifically, Cubist explained, "the patentees erred in describing one amino acid's stereochemistry as 'L-Asn' in the tail of the compound illustrated in Formula 3, when the correct stereochemistry of the disclosed and claimed amino acid is 'D-Asn.'" Cubist further explained that the true nature of the stereochemistry of daptomycin was disclosed in a 2005 journal article by Vivian Miao *et al*. The Miao article, Cubist stated, "demonstrates that the A-21978C factors of Formula 3 inherently contain the 'D-Asn' in the tail portion illustrated in Formula 3 when isolated from their native source, not an 'L-Asn.'"

The examiner concluded that it was appropriate to use a certificate of correction to correct the error identified by Cubist. Accordingly, the examiner issued the certificate, correcting the diagram of Formula 3 in the specification and four of the claims of the '071 patent by substituting "D-Asn" for "L-Asn" in the diagram.

2

Before the district court, Hospira argued that the PTO had erred by issuing the certificate of correction because the change in the structural diagram of Formula 3 altered the substance of the claims, broadening their reach. Accordingly, Hospira argued, the '071 patent should be construed to be limited to the variant of the daptomycin compound containing the L-isomer of asparagine. The compound with the L-isomer of asparagine is an antibiotic, but a much less potent one than daptomycin.

Hospira's expert testified that Formula 3 with the L-isomer of asparagine was an entirely different compound

from Formula 3 with the D-isomer of asparagine. He therefore concluded that the asserted claims did not read on daptomycin. The expert admitted, however, that he had not considered the specification of the '071 patent in reaching his determination that the certificate of correction had the effect of broadening the claims of the patent to read on daptomycin for the first time.

Cubist's expert testified that the specification made it clear that the claims of the '071 patent were directed to daptomycin, not to the variant containing the L-isomer of asparagine. Because it was plain that the claims were directed to daptomycin, Cubist argued, it was appropriate for the PTO to correct the error in the structural diagram of Formula 3.

The district court acknowledged that the chemical structure of Formula 3 in the corrected version of the '071 patent is different from that of the pre-correction version of the patent. However, the court characterized the PTO's action as simply correcting an error in the diagram of Formula 3 without changing the scope of the patent. The court agreed with Cubist that the specification made clear that the patent claimed the daptomycin compound all along; the pre-correction version merely misidentified the stereoisomer of the asparagine amino acid found in that compound.

Based on the evidence summarized above, the district court concluded that Hospira had not satisfied its burden to show that the certificate of correction was invalid. In particular, the court ruled that the specification as a whole "confirms that the Formula 3 compound identified in the claims is truly D-asparagine daptomycin, the by-product of the fermentation process" described in the specification. Accordingly, the court held, substituting L-asparagine for D-asparagine in the Formula 3 chemical structure was "a correction of minor character because it did not result in 'the new version cover[ing] territory the

old one did not.'" Contrary to Hospira's contention, the court explained, "D-asparagine was covered both before and after correction."

3

On appeal, Hospira argues that the change in the '071 patent made by way of the certificate of correction was not a change "of minor character," as provided for in section 255, because the change broadened the scope of the asserted claims. *See Superior Fireplace Co. v. Majestic Prods. Co.*, 270 F.3d 1358, 1375 (Fed. Cir. 2001) ("A mistake that, if corrected, would broaden the scope of a claim must thus be viewed as highly important and thus cannot be a mistake of 'minor character.'"). In Hospira's view, because the change from L-Asn to D-Asn in the structural diagram broadened the scope of the claims to read on daptomycin rather than the L-Asn variant of daptomycin, the certificate of correction was invalid.

Once the PTO has issued a certificate of correction, a court may invalidate the certificate only upon a showing of clear and convincing evidence that it was improperly issued. *Superior Fireplace Co.*, 270 F.3d at 1367. In this case, no such showing has been made.

The problem with Hospira's argument is that the district court did not view the change in the diagram as changing the scope of the claims at all. Instead, the court regarded the change as simply conforming the structural diagram of Formula 3 to the compound described in the specification and covered by the claims.

Contrary to Hospira's argument, the original structural diagram in the '071 patent did not establish that the patent was directed to a compound other than daptomycin. As this court has noted, a chemical structure is "simply a means of describing a compound; it is not the invention itself." *Regents of Univ. of N.M. v. Knight*, 321 F.3d 1111, 1122 (Fed. Cir. 2003). In determining what

compound the patent claims were directed to, the proper focus is not limited to the chemical structure depicted in the diagram. Instead, the specification as a whole must be considered. As the district court explained, the Formula 3 compound is defined not only by the structural diagram, but also by other portions of the specification.

The specification of the '071 patent does not rely exclusively on the structural diagram of Formula 3 to describe the subject compound. By reference to a co-pending application (later issued as U.S. Patent No. 4,885,243), the specification teaches that daptomycin is obtained through fermentation of *Streptomyces roseosporus*. That fermentation process necessarily results in daptomycin, not the variant with the L-isomer of asparagine. The evidence at trial established that the L-isomer variant cannot be produced by fermentation and can only be produced synthetically.

In addition, the specification describes the claimed compound by the code name given to it by Lilly—the designation LY146032. Evidence introduced by Cubist at trial showed that the code name LY146032 refers to daptomycin, not the variant of daptomycin with the L-isomer of asparagine.

Finally, at the time of the original application that matured into the '226 patent, it was universally believed that the asparagine amino acid in daptomycin was the L-isomer of asparagine, not the D-isomer. It was not until well after the filing of the original '226 patent (in 1991), the issuance of that patent (in 1999), and the filing of the reissue application (in 2000) that Lilly researchers determined that the previous understanding of the structure of daptomycin was mistaken, and that the asparagine amino acid in daptomycin is the D-isomer of asparagine, not the L-isomer, as previously thought. Even though researchers had previously been mistaken about the precise chemical structure of daptomycin, it was nonetheless

clear from the specification that the patentees possessed daptomycin (with the D-isomer of asparagine) and that the references to Formula 3 in the claims of the '071 patent were directed to daptomycin.

4

Hospira relies heavily on this court's decision in *Bayer v. Dow Agrosciences LLC*, 728 F.3d 1324 (Fed. Cir. 2013). That case, however, is different in important ways from this one. The patentee in *Bayer* claimed, in pertinent part, a recombinant gene comprising a DNA sequence encoding for a polypeptide "having the biological activity of 2,4-D monooxygenase." *Id.* at 1326. Although it was determined long before Bayer's patent issued that the gene Bayer had sequenced encoded for an enzyme that was a dioxygenase, not a monooxygenase, Bayer did not seek to change the claim language to reflect the error. Instead, Bayer argued that the claim language should be interpreted to cover any DNA sequence that codes for an enzyme that alters a common herbicide known as 2,4-D by cleaving its side chain, regardless of whether the cleaving enzyme is a monooxygenase or a dioxygenase. *Id.* at 1327.

This court rejected that argument as a matter of claim construction. We explained that Bayer's proposed construction would be inconsistent with the "strong accepted scientific meaning" of the claim language by "strip[ping] the monooxygenase half of the claim phrase of its accepted descriptive meaning" and "assert[ing] a specification 'definition' of the biological-activity half." 728 F.3d at 1330. Beyond that, Bayer's proposed claim construction would have raised serious doubts about the validity of Bayer's claim by broadening the claim to cover the enzymatic function of causing the cleavage of the side chain of 2,4-D, but not "providing even an indirect structural identification of all that would be within the claim's scope." *Id.* at 1331.

In this case, unlike in *Bayer*, the applicants sought a certificate of correction to correct the structural diagram, which was based on a previous misunderstanding of the chemical structure of the claimed compound. Given the other descriptions of the claimed compound in the specification, the PTO and the district court concluded that the reference to the L-isomer of asparagine was an error and that the claimed compound was the compound with the D-isomer of asparagine. In *Bayer*, by contrast, the patentee sought a broad, functional claim construction based on the original claim language. We found that claim construction to be seriously flawed and rejected it. Given the very different approaches employed by the patentees in the two cases, as well as the strong indications in the specification of the '071 patent that Formula 3 was in fact daptomycin (despite the error in the structural diagram), the outcome of this case is not controlled by *Bayer*.

In light of the heavy burden on a party seeking to invalidate a certificate of correction, we uphold the district court's conclusion that the certificate of correction did not alter the scope of the patent, but merely corrected an error as to the chemical structure of daptomycin. We therefore reject Hospira's argument that the asserted claims of the '071 patent should be limited to the variant of daptomycin containing the L-isomer of asparagine.

B

Hospira next argues that if the validity of the certificate of correction is sustained, the asserted claims of the '071 patent should be held invalid for violating the written description requirement of 35 U.S.C. § 112. Like the district court, we reject that argument, and for the same reasons.

Hospira contends that the written description requirement was not satisfied because the specification did not disclose the features or structure of daptomycin (containing the D-isomer of asparagine), and thus the

specification provided no indication that the inventors knew they were working with daptomycin having that structure.

The district court found as a matter of fact that the disclosure of the specification reasonably conveyed to those skilled in the art that the inventors had possession of the claimed subject matter as of the filing date, i.e., that the specification described "an invention understandable to [a] skilled artisan and show[ed] that the inventor actually invented the invention claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Notwithstanding the error in the structural diagram of Formula 3, the court concluded that one skilled in the art would have understood that the inventors possessed and were working with the naturally occurring fermentation product, i.e., the daptomycin molecule containing D-asparagine. For that reason, the court held that Hospira had failed to show, by clear and convincing evidence, that the '071 patent was invalid for lack of an adequate written description.

Hospira has not shown that the district court committed clear error in finding that the written description requirement was satisfied. The references in the specification to the "A21978C cyclic peptide," and to LY146032, Lilly's codename for daptomycin, would have demonstrated to a person of skill in the art that the inventors were in possession of daptomycin, the product of the fermentation of *Streptomyces roseosporus*, in spite of the error in the structural diagram.

The fact that the inventors were mistaken as to one aspect of the structure of daptomycin at the time the application for the original '226 patent was filed does not render the specification inadequate to satisfy the written description requirement. It was enough that the specification disclosed relevant identifying characteristics that distinguished daptomycin from other compounds and thus

showed that the inventors had possession of daptomycin, even though they may not have had an accurate picture of the entire chemical structure of that compound. *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1072 (Fed. Cir. 2005).

Hospira relies on *In re Wallach*, 378 F.3d 1330 (Fed. Cir. 2004), in support of its written description argument, but that case has little in common with this one. In *Wallach*, the applicants were in possession of only about 5% of the amino acids of the nucleic acid encoding a particular protein, but they sought to claim all DNA molecules that would code for the protein. That is, they claimed the entire nucleotide sequence of any DNA molecule that would code for the protein, even though they were in possession of only a small portion of one such nucleotide sequence. This court upheld the PTO's decision rejecting the applicants' claims.

The applicants in *Wallach* argued that they were entitled to patent protection for the claimed DNA molecules because they had shown that they were in possession of the protein. This court noted, however, that whether the applicants "were in possession of the protein says nothing about whether they were in possession of the protein's amino acid sequence." 378 F.3d at 1334.

Because the applicants had not "provided any evidence that the full amino acid sequence of a protein can be deduced from a partial sequence and the limited additional physical characteristics that they have identified," the court concluded that the applicants had not shown that they were in possession of the claimed nucleic acid sequences. *Id.* at 1335. The court summed up its ruling by stating that the applicants had not shown "that there is any known or disclosed correlation between the combination of a partial structure of a protein, the protein's biological activity, and the protein's molecular weight, on

the one hand, and the structure of the DNA encoding the protein on the other." *Id.*

In this case, the applicants claimed only what they had produced—the daptomycin molecule—which they identified in several ways. The district court found that the identification of the molecule in the specification was sufficient to inform a person skilled in the art that the inventors were in possession of the daptomycin molecule, even though the structure that they ascribed to it was inaccurate in one respect. The description of the molecule provided in the specification in this case was far greater than the very limited description of the DNA sequence in the *Wallach* case, and the claims in this case, unlike those at issue in *Wallach*, were limited to the compound itself. We therefore uphold the district court's finding that the specification of the '071 patent contained the written description required by 35 U.S.C. § 112 and that the asserted claims are not invalid for lack of adequate written description.

C

Finally, Hospira argues that the asserted claims of the '071 patent are invalid because they violate the "recapture rule" applicable to reissued patents. Relying on the proposition that a patentee may not "regain[] through reissue the subject matter that he surrendered in an effort to obtain allowance of the original claims," *Pannu v. Storz Instruments, Inc.*, 258 F.3d 1366, 1370-71 (Fed. Cir. 2001), Hospira argues that the claims of the reissued '071 patent are impermissibly broader than the corresponding original claims of the '226 patent.

The recapture rule applies if (1) the reissue claims are broader than the original patent claims; and (2) the broader aspects of the reissued claims relate to subject matter that was surrendered in the prosecution of the original patent. *In re Youman*, 679 F.3d 1335, 1345 (Fed. Cir. 2012); *In re Mostafazadeh*, 643 F.3d 1353, 1358 (Fed.

Cir. 2011); *In re Clement*, 131 F.3d 1464, 1469 (Fed. Cir. 1997). The recapture rule does not apply if the reissue claims were materially narrowed compared to the original claims "such that full or substantial recapture of the subject matter surrendered during prosecution is avoided." *In re Mostafazadeh*, 643 F.3d at 1358. Moreover, the recapture rule applies only if the patentee surrendered subject matter in the original prosecution in order to overcome a prior art rejection. *In re Clement*, 131 F.3d at 1469.

The reissue claims here did not violate the recapture rule. Besides the fact that reissue claims 18 and 26 are narrower than original claim 24 by requiring the presence of the Formula 1 and Formula 2 compounds, which are not required by original claim 24, the evidence shows that the applicants did not surrender subject matter in the prosecution of the '226 patent to avoid prior art.

In the course of the prosecution of the application that matured into the '226 patent, the examiner rejected claim 24 on three occasions, each time on indefiniteness grounds. In response to the third rejection, the applicants cancelled claim 24. Although the applicants stated that claim 24 was nonobvious, that statement was made in the context of an argument that a large number of the claims of the application, including claim 24, were nonobvious. The applicants did not cancel the other claims, but they cancelled claim 24, which was the only claim rejected on indefiniteness grounds. The applicants ultimately succeeded in overcoming the obviousness objection to the other claims.

The prosecution history thus makes it clear that the applicants withdrew claim 24 from the application because of the indefiniteness rejection, not to avoid prior art. Accordingly, the recapture rule does not render claims 18 and 26 of the '071 patent invalid.

For the foregoing reasons, we hold that the asserted claims of the '071 patent are not invalid. Because Hospira does not contest the district court's ruling that its products infringe the '071 claims if the certificate of correction was properly issued and the patent is otherwise valid, we sustain the district court's judgment of infringement as to the '071 patent.

II

Cubist has cross-appealed from the portions of the district court's judgment invalidating the other four patents at issue in this case: the two patents that the district court referred to as the "dosing patents" (the '967 patent and the '689 patent) and the two patents that the district court referred to as the "purity patents" (the '238 patent and the '342 patent). We affirm the district court's decision that all four of those patents are invalid for obviousness.

A

1

In the 1980s, Lilly researchers who were looking for an antibiotic effective against *Staphylococcus aureus* ("*S. aureus*") infections discovered daptomycin. At the time, Lilly's drug vancomycin was the only available treatment for infections caused by methicillin-resistant *S. aureus* bacteria. While sufficiently high doses of daptomycin proved effective against such infections, the researchers discovered that high doses of daptomycin administered every twelve hours resulted in skeletal muscle toxicity in some patients. When the Lilly researchers encountered the toxicity problem, they suspended further testing of daptomycin.

Cubist subsequently licensed the daptomycin compound from Lilly and conducted studies designed to overcome the problem of skeletal muscle toxicity that Lilly had encountered. Cubist researchers discovered

that the toxic side effects of daptomycin could be reduced by administering the drug less frequently than twice daily. They subsequently sought patent protection for treatment methods involving large doses of daptomycin and large intervals between doses.

2

Asserted claims 16, 17, 34, and 35 of the '967 patent and asserted claims 51 and 52 of the '689 patent recite dosage regimens. The claims of the '967 patent recite a method of administering daptomycin at a dosage interval that minimizes skeletal muscle toxicity; the recited dosage is 4 or 6 milligrams per kilogram of patient weight (abbreviated as "mg/kg") and the recited dosage interval is once every 24 hours. The claims of the '689 patent recite administering daptomycin in doses of 4 or 6 mg/kg once every 48 hours.

At trial, Hospira sought to prove that the asserted claims of the '967 patent are anticipated by a 1991 journal article by James Woodworth *et al.* The Woodworth article stated that, based on the pharmacokinetics and antibacterial activity of daptomycin, "doses of 4 to 6 mg/kg/day, possibly in divided doses, are predicted to be effective." The article added that the reported data "suggest that good antibacterial activity would be produced from single doses of 4 to 6 mg/kg," and that the drug's long half-life in the body would "allow[] once- or twice-daily administration with the proper doses."

Although the Woodworth article did not mention the objective of minimizing skeletal muscle toxicity, the district court found that the effect of minimizing skeletal toxicity was inherently disclosed by Woodworth's suggestion to administer 4 or 6 mg/kg of daptomycin once a day. That is, the court found that minimizing skeletal toxicity was "a necessary accompaniment to the other disclosed claimed limitations and therefore was inherently disclosed by the Woodworth article."

In response to Cubist's argument that the Woodworth article was not enabling, the court found that Woodworth "identified the *exact* dosage amounts and interval claimed by the '967 patent: 4 mg/kg/day and 6 mg/kg/day." The dosage level and timing, the court found, "were two major variables that required no additional experimentation." Accordingly, the court found that Cubist had failed to rebut the presumption that the Woodworth article enabled the disclosed invention.[3]

The court also found the asserted claims of the '967 patent to be invalid for obviousness based on the Woodworth article and the '226 patent, in view of the known properties of daptomycin. The court explained that the Woodworth article and the '226 patent contained disclosures "indicating that the claimed dosage levels would be effective." Beyond that, the known properties of daptomycin provided "additional support for why one skilled in the art would find daily dosing to be preferable and obvious." In particular, the court found, it was known that daptomycin's effectiveness is concentration-dependent, which suggests that less frequent and more concentrated treatments would be more effective than smaller doses of the drug administered at more frequent intervals.

The court reached the same conclusion with respect to the '689 patent, which provides for doses of daptomycin to be administered every 48 hours. The court explained that a person of skill in the art would know that in treating patients with impaired renal function, either the doses would have to be reduced or the dosage intervals increased. In light of the concentration-dependent killing capacity of daptomycin, the court concluded, it would have

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[3] Hospira argued that the '226 patent also anticipated the asserted claims of the dosing patents, but the district court rejected that argument.

been obvious to consider doubling the dosage interval for a patient with impaired kidney function, such as 50% of normal.

Finally, the district court analyzed the secondary considerations invoked by Cubist, but found them insufficient to overcome the showing of obviousness based on the cited prior art references.

3

Focusing largely on the Woodworth reference, Cubist challenges the district court's ruling that the asserted claims of the dosing patents would have been obvious. We hold that the district court did not commit legal error and that the findings underlying the court's obviousness ruling were not clearly erroneous. Because we uphold the district court's obviousness ruling with respect to the dosing patents, it is not necessary for us to address Cubist's challenge to the court's ruling on anticipation.

In challenging the district court's finding of obviousness, Cubist places great weight on the fact that the Woodworth reference does not mention skeletal muscle toxicity. In addition, Cubist argues that the court's reliance on the once-daily administration of other similar antibiotics to reduce toxic side-effects is too remote to support the court's obviousness finding as to the once-daily administration of daptomycin. Finally, Cubist complains that the district court ignored secondary evidence of non-obviousness, including evidence of long-felt but unmet need, failure of others, commercial success, and unexpected results.

4

Cubist did not discover daptomycin, nor did it invent the use of daptomycin for treating bacterial infections. Beginning in the 1980s, Lilly tested daptomycin treatment protocols including once-daily doses of 2mg/kg, and twice-daily doses of 3 mg/kg. Both of those protocols were

determined to be effective against some infections, although they were not as effective as conventional therapies in treating the most serious targeted infection, *S. aureus* endocarditis ("SAE"). Lilly researchers concluded that the dosages used in those studies did not result in enough free daptomycin in the bloodstream to kill the targeted bacteria. Lilly conducted a follow-up study in which subjects were given up to 4 mg/kg of daptomycin every 12 hours. At that dosage level, however, several subjects developed symptoms of skeletal muscle toxicity, and the study was abandoned.

The dosing patents proposed the administration of doses of either 4mg/kg or 6mg/kg, similar to the dosage in the Lilly follow-up study, but given only once per day or once every 48 hours. Given what was previously known about daptomycin and related compounds, the district court reasonably concluded that the treatment protocols claimed in the dosing patents would have been obvious in light of the prior art.

As the district court observed, the Woodworth article clearly pointed to the use of once daily administration of daptomycin in doses of 4 to 6 mg/kg per day. It did so in the abstract of the article, where the authors predicted that doses of 4 to 6 mg/kg per day would be expected to be effective either in single doses or "possibly in divided doses." It also did so in the body of the article, where the authors specifically noted that the long half-life of daptomycin would allow the administration of daptomycin once or twice a day, and that anti-bacterial effects could be achieved from single daily doses of 4mg/kg to 6 mg/kg, exactly the doses set forth in the dosing patents. Similarly, the '226 patent discloses that a "typical daily dose for an adult human" of about 1.4 mg/kg to 14 mg/kg "can be administered as a single daily dose or in multiple doses per day." '226 patent, col. 10, ll. 56-61. The district court found that the '226 patent, like the Woodworth article,

disclosed that the claimed dosage levels would be effective, "either through daily or divided administrations."

Cubist takes issue with the Woodworth reference on two grounds: first, that it is based on laboratory studies, not clinical trials, and is thus predictive in nature with respect to the likely effects of the drug in patients; and second, that it does not advert to minimizing skeletal muscle toxicity, which is an objective expressly set forth in the asserted claims.

While it is true that the Woodworth reference is predictive in nature, it is based on extensive laboratory research, and its predictions of the efficacy of a dosage regimen of 4 mg/kg to 6 mg/kg at daily intervals give rise to a reasonable expectation that dosages in that amount would be effective in patients. Moreover, published accounts of Lilly's clinical trials indicated a dosage level of 2 mg/kg administered once daily produced no reported side effects and a dosage level of 3 mg/kg administered twice daily produced no symptoms of skeletal muscle toxicity, but were not highly effective against SAE. Those results would have given rise to a reasonable expectation that somewhat higher doses administered less frequently than twice daily could be expected to be both safe and effective.

The district court's obviousness finding is also supported by evidence of the known properties of daptomycin, from which persons of skill in the art could reasonably conclude not only that doses given once per day or even less frequently would be effective, but also that increased dosage intervals would result in less risk of skeletal muscle toxicity.

That evidence included four characteristics of daptomycin that suggested the use of high dosages of daptomycin with long intervals between doses. First, daptomycin is especially effective at killing bacteria when it is found in high concentrations in the patient's body.

Second, daptomycin has a long half-life, which allows it to act in the body over an extended period of time before being cleared by the kidneys. Third, daptomycin has a long post-antibiotic effect, i.e., it continues to suppress bacteria after leaving the body. Those three characteristics suggest that it is not necessary to administer daptomycin frequently. Fourth, muscle toxicity resulting from daptomycin was known to be reversible in most cases. That characteristic suggests that administering doses at greater intervals would allow the muscles more time to repair between doses, thus reducing the cumulative toxic effect of the drug.

The district court's finding is also supported by evidence pertaining to aminoglycosides, a group of antibiotic compounds similar to daptomycin. The court found aminoglycosides to be "within the relevant prior art" that "would have been considered by one skilled in the art," and it found that aminoglycosides share many properties with daptomycin. Like daptomycin, aminoglycosides exhibit concentration-dependent killing, long-lasting post-antibiotic effects, and reversible toxicity. And the evidence showed that less frequent dosing resulted in the avoidance of toxicity problems with aminoglycosides. Those characteristics, the district court found, would have led one of skill in the art to believe that increasing the dosage intervals for daptomycin would give rise to a reasonable expectation of increased efficacy while minimizing the toxic side effects of the drug.

Cubist does not separately argue the validity of the asserted claims of the '689 patent; in any event, however, we agree with the district court that those claims, which recite dosage intervals of 48 hours, would have been obvious based on the same analysis that applies to the claims of the '967 patent. The '689 patent notes that longer dosage intervals are appropriate for patients with impaired renal function or requiring dialysis. '689 patent, col. 5, line 63, to col. 6, line 5. The district court explained

that it is known that patients with compromised renal function do not clear drugs such as daptomycin from their systems as quickly as persons with healthy kidneys. Accordingly, it was reasonable for the court to conclude that a person of skill in the art would expect that for such a patient a longer dosage interval would be equally effective against bacteria and would be necessary to avoid building up concentrations of daptomycin in the patient's body that could lead to skeletal muscle toxicity.

5

Cubist relies heavily on secondary consideration evidence to support its argument that the asserted claims of the dosing patents would not have been obvious. The district court acknowledged that secondary consideration evidence must be weighed in the obviousness analysis, but the court concluded that "any weight certain factors may have does not overcome Hospira's *prima facie* showing of obviousness."

Cubist argues that, prior to the invention claimed in the dosing patents, there was a long-felt but unmet need for such a treatment regimen and that the success of Cubist's invention was unexpected. As the district court pointed out, however, daptomycin treatment regimens that were only slightly different from Cubist's had previously been shown to be effective against a variety of bacterial infections. Although the prior art daptomycin treatment methods had not proved effective for SAE, the court noted that SAE is the target infection in only about 5% of the cases in which daptomycin is administered. Accordingly, the court concluded that any "long-felt need" or "unexpected results" applied only to the small percentage of cases in which daptomycin was used to treat SAE.

The court made the same observation with regard to Cubist's argument regarding the commercial success of Cubist's daptomycin product, Cubicin. Although Cubist attributes the success of Cubicin to the invention of the

'967 and '689 patents, the district court concluded that Cubicin's commercial success is mainly attributable to daptomycin itself; it is attributable only in small measure to the dosage and interval protocols disclosed in the dosing patents. For Cubicin's use in treating other infections that make up the bulk of the market, the court found, "Cubist was unable to establish that the claimed features drove market success." The court likewise found that any "unexpected results" obtained from the dosing patents were limited to the treatment of serious infections such as SAE.

Cubist sought to show the failure of others by pointing to Lilly's failure to develop the dosing regimens set forth in the dosing patents. The court, however, found that Cubist's showing was undercut by the fact that Lilly owned and marketed vancomycin, which was regarded as the "gold standard" for treating many serious infections such as infections caused by methicillin-resistant *S. aureus* bacteria. Referring to vancomycin, Hospira's expert on secondary considerations testified that Lilly "had a drug that was generating four to five hundred million dollars a year in the late eighties and early 1990s. They would have very little incentive to cannibalize those sales by the introduction of a substitutable drug." Therefore, the court concluded, "economic considerations, and not merely difficulties in the lab, weighed on Eli Lilly's decision to 'shelve' daptomycin development."

We are not persuaded that the district court committed legal error in its analysis of the secondary consideration evidence. The court weighed the secondary consideration evidence against the other evidence of obviousness and concluded that the secondary consideration evidence was not sufficiently strong to overcome the showing of obviousness arising from an analysis of the prior art. That conclusion was not clearly erroneous. We therefore sustain the district court's judgment that the

asserted claims of the dosing patents are invalid for obviousness.

B

The second portion of Cubist's cross-appeal is its challenge to the district court's ruling that the asserted claims of the purity patents (the '238 and '342 patents) are invalid. The district court held that claim 98 of the '238 patent is anticipated by Lilly's U.S. Patent No. 4,874,843 ("the '843 patent"), and that all of the asserted claims of the two purity patents are invalid for obviousness. Because we sustain the district court's ruling that all of the asserted claims of the purity patents are invalid on grounds of obviousness, we do not need to address the issue of anticipation.

1

Of the three asserted claims of the '238 patent, claim 91 recites a method of preparing a pharmaceutical daptomycin composition that is essentially free of each of 14 identified impurities, i.e., in which the composition has less than 0.5% of each impurity and is obtained by a process comprising the step of forming an aggregate containing daptomycin. Claim 98 recites a daptomycin composition that is at least 93% pure, in which the composition is obtained by the steps of forming a daptomycin aggregate, separating the aggregate from low molecular weight contaminants, causing the aggregate to dissociate into monomers, and separating the daptomycin monomers from high molecular weight contaminants by a size selection technique of either ultrafiltration or size exclusion chromatography. Claim 187 recites a daptomycin composition that is at least 97% pure relative to certain daptomycin-related impurities, in which the composition is obtained from a lipopeptide aggregate containing daptomycin.

Of the two asserted claims of the '342 patent, claim 23 recites a pharmaceutical daptomycin composition that is at least 93% pure with respect to certain daptomycin-related impurities and has less than 4% each of anhydro-daptomycin and the beta isomer of daptomycin, in which the composition is prepared by a process comprising the steps of subjecting the daptomycin to anion exchange chromatography, forming a daptomycin aggregate, and obtaining the daptomycin from the daptomycin aggregate by a method comprising the steps of filtering the daptomycin aggregate so that the aggregate is retained on the filter and collecting the aggregate. Claim 53 recites a daptomycin lyophilized powder pharmaceutical composition that is 94 to 96% pure relative to certain daptomycin-related impurities and has less than 1% of the lactone hydrolysis product of daptomycin and less than 4% each of anhydro-daptomycin and the beta isomer of daptomycin, in which the composition is prepared by a process comprising the steps of forming a daptomycin aggregate, converting the aggregate to monomers by a process including either anion exchange chromatography or hydrophobic interaction chromatography.

2

In its obviousness analysis, the court focused on the two primary purification steps recited in the asserted claims: (1) micelle or aggregation filtration and (2) anion exchange chromatography. Those steps, the court explained, enable the daptomycin to be separated from impurities such as saponins and endotoxins. Saponins are found in the soy commonly used in daptomycin fermentation, and endotoxins are segments of the cell walls of certain bacteria that are left over after the fermentation process that is used to produce daptomycin.

With respect to micelle filtration, the district court explained that in an acidic solution, daptomycin forms micelles, or aggregates, of daptomycin molecules. The

formation of the micelles effectively increases the size of the particles of daptomycin, so that the daptomycin will not pass through the pores of certain filters. Because smaller impurities such as saponins can pass through the filters and be discarded, the process of forming micelles enables the filters to separate the saponins from the daptomycin.

After that filtration step is completed and the saponins are discarded, the solution is neutralized. That step causes the daptomycin aggregates to break apart into individual daptomycin molecules, which are small enough to pass through the filters' pores. Larger molecules, such as endotoxins, cannot pass through the filters, resulting in the separation of the daptomycin from the endotoxins. As a result of the two-step filtering process, the daptomycin solution is free of both saponins and endotoxins.

The district court held that the use of micelle filtration would have been obvious to a person of skill in the art based on two references: a 1997 publication by Sung-Chyr Lin *et al.* that showed that it was possible to employ micelle filtration for the recovery and purification of most surfactants; and a 1988 reference by Jeremy H. Lakey *et al.* teaching one skilled in the art that daptomycin displays the properties of a surfactant.

With respect to anion exchange chromatography, the district court found that the technique was a familiar one, and that it was well understood in the industry that it could be used to filter out impurities similar to daptomycin in size but differing in chemical structure. The court found that anion exchange chromatography would have been an obvious method of purification to one of skill in the art after solving the problem of removing saponins.

As in the case of the dosing patents, the court reviewed Cubist's secondary consideration evidence in detail and concluded that the secondary consideration evidence did not undermine Hospira's showing that the

purity patents would have been obvious to a person of skill in the art. Accordingly, the court held the asserted claims of the purity patents invalid for obviousness.

3

In its brief, Cubist does not directly address the district court's analysis of the micelle filtration and anion exchange chromatography limitations of the asserted claims. Instead, Cubist argues that the court failed to analyze obviousness on a claim-by-claim basis and failed to conduct an analysis of each of the limitations of the asserted claims. In doing so, Cubist asserts, the court "did not address a number of limitations that were material to the obviousness analysis." Focusing on claim 187 of the '238 patent and claims 23 and 53 of the '342 patent, Cubist argues that the court ignored the claim limitations requiring greater than 93% purity with respect to daptomycin-related substances. Cubist also contends that the district court ignored the requirement of claim 91 of the '238 patent that the daptomycin be "essentially free" of 14 daptomycin-related impurities, which has the effect of requiring that the claimed daptomycin composition contain no more than 0.5% of each of the impurities referred to in the patent. *See* '238 patent, col. 7, ll. 52-56.

Although the district court focused on the two limitations relating to the mechanics of the purification process, the court's focus on those limitations does not undermine its obviousness analysis. The use of the two techniques set forth in those limitations—micelle filtration and anion exchange chromatography—are the keys to the purification process described in the specifications of the purity patents and recited in each of the asserted claims. The purity patents do not point to any additional techniques that are necessary to obtain the recited purity levels in each of the claims. Once the saponins and endotoxins are eliminated from the daptomycin composition by micelle filtration, the desired purification levels can be obtained

by what the district court referred to as "the simple concept" of ion exchange purification.

Cubist contrasts its purification process with the process used by Lilly, which is described in Lilly's '843 patent. That process produced daptomycin that was approximately 93% pure relative to daptomycin-related impurities. Cubist argues that its claimed process of micelle filtration followed by anion exchange chromatography constituted a breakthrough for the purification of daptomycin compositions, providing a means both for filtering out endotoxins and saponins, and for obtaining levels of purity relative to daptomycin-related substances that were significantly higher than the 93% achieved by Lilly's process.

Although Cubist argues that the techniques for obtaining purity levels of up to 97% with respect to daptomycin-related substances (as in claim 187 of the '238 patent) and levels of less than 0.5% for each of 14 daptomycin-related impurities (as in claim 91 of the '238 patent) would not have been obvious, the district court found that it would have been obvious to use both micelle filtration and anion exchange chromatography and that by using those steps the desired purity levels could easily be achieved.

The court's obviousness finding as to micelle filtration was soundly based on its reliance on the Lin and Lakey prior art references. Given the similarities between daptomycin and surfactants, and the known utility of micelle filtration of surfactants, the court permissibly found that a person of skill in the art would have looked to micelle filtration to remove saponins and endotoxins from the daptomycin composition.

The court's findings as to the obviousness of anion exchange chromatography were also well supported. Based on evidence that ion exchange chromatography "was known to be one of the most common purification tech-

niques in the field," the court found that ion exchange techniques, and in particular anion exchange chromatography, "would have been an obvious method of purification to one skilled in the art, after solving the problem of removing saponins." That technique, the court found, could produce the high purity levels recited in each of the asserted claims.[4] The court rejected Cubist's argument that those skilled in the art believed there was an upper limit on the obtainable purity level of daptomycin, a belief that that would have "discouraged one skilled in the art from applying a common purification technique after the saponin problem was resolved." The court's findings as to anion exchange chromatography and the purity results obtainable from its use were not clearly erroneous.

4

Finally, Cubist argues that the district court erred by failing to give sufficient weight to the secondary considerations of nonobviousness, in particular the long-felt need for a commercial-scale purification process for daptomycin and the unexpected result that daptomycin would form

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[4] Cubist complains that by referring to the observation in the purity patents that "running samples obtained via the '843 Patent process through an anion exchange column yielded a very high purity," the district court improperly relied on disclosures in the patent in suit to buttress the case of obviousness. To the contrary, the court made the observation about the high purity levels obtained by anion exchange chromatography to show that once the saponins had been removed by micelle filtration, that well-known technique was sufficient by itself to achieve the purity levels claimed in the purity patents, and that the purity patents added nothing to what was known in the art. As the court explained, the purity patents "do not claim anything other than this simple concept."

reversible micelles under conditions compatible with purification.

The district court considered the evidence of secondary considerations but did not find that evidence sufficiently strong to overcome the proof of obviousness based on the prior art. As for Cubist's claim that there was a long-felt need for a commercial-scale purification process for daptomycin, the court noted that the asserted claims did not refer to production-scale purification, but were simply directed to purification "whether produced in an economical or wasteful manner." The court added that it was not persuaded by Cubist's argument that there was a long-felt need for an efficient method of purifying daptomycin, particularly in light of the evidence that many believed daptomycin was a "dead drug."

As for Cubist's assertion that the propensity to form micelles was an unexpected property of daptomycin, the district court acknowledged that "Cubist's being the first to observe daptomycin's micelle-forming properties offers some objective evidence of non-obviousness." However, in light of the evidence that it was known that daptomycin behaves like surfactants, which in turn were known to form micelles, the court concluded that the unexpected results argument was not "entitled to serious weight." Ultimately, the court found that the secondary considerations relied on by Cubist were not sufficiently strong to "upset Hospira's *prima facie* showing that the asserted claims of the purity patents are obvious."

We sustain the district court's determination that the secondary consideration evidence did not overcome the showing of obviousness based on the prior art. With respect to Cubist's claim of a long-felt need, the evidence showed that Lilly's decision not to pursue its research into daptomycin was based on economic considerations, not on the absence of methods of obtaining sufficiently high purity levels. With respect to Cubist's claim that it was

unexpected that daptomycin would form "reversible micelles," the district court did not clearly err in rejecting that argument in light of the Lakey reference that taught that daptomycin behaves like a surfactant and the Lin reference that taught that surfactants form micelles under the proper conditions. We therefore uphold the district court's ruling that the asserted claims of Cubist's purity patents are invalid for obviousness.

Each party shall bear its own costs for these appeals.

AFFIRMED