United States Court of Appeals for the Federal Circuit

CADENCE PHARMACEUTICALS INC.
SCR PHARMATOP,
Plaintiffs-Appellees

v.

EXELA PHARMSCI INC., EXELA HOLDINGS INC., EXELA PHARMA SCIENCES LLC,
Defendants-Appellants

2014-1184

Appeal from the United States District Court for the District of Delaware in No. 1:11-cv-00733-LPS, Judge Leonard P. Stark.

Decided: March 23, 2015

KENNETH G. SCHULER, Latham & Watkins LLP, Chicago, IL, argued for all plaintiffs-appellees. Plaintiff-appellee Cadence Pharmaceuticals Inc. also represented by MARC NATHAN ZUBICK, EMILY C. MELVIN; STEPHEN P. SWINTON, DARRYL HUGH STEENSMA, San Diego, CA; RICHARD P. BRESS, GABRIEL BELL, Washington, DC; PARKER TRESEMER, Costa Mesa, CA. Plaintiff-appellee SCR Pharmatop represented by CHARLES A. WEISS, Holland & Knight, LLP, New York, NY.

JEFFREY STEPHEN WARD, Merchant & Gould PC, Madison, WI, argued for defendants-appellants. Also represented by WENDY M. WARD; CLARENCE EDWARD POLK, JR., Polk & Chintapalli, PLLC, Ashburn, VA,; SATISH CHANDRA CHINTAPALLI, Cary, NC.

Before REYNA, LINN, and WALLACH, *Circuit Judges.*

LINN, *Circuit Judge.*

In this Hatch-Waxman Act litigation, Exela PharmSci Inc., Exela Holdings, Inc. and Exela Pharm Sciences, LLC (collectively "Exela") appeal the district court's construction of certain claim terms of U.S. Patents No. 6,028,222 (the "'222 patent") and No. 6,992,218 (the "'218 patent"), *Cadence Pharm., Inc. v. Paddock Labs. Inc.*, 886 F. Supp. 2d 445 (D. Del. 2012), and its rulings that Exela infringed certain asserted claims of both patents and failed to prove invalidity as to the '218 patent. *Cadence Pharm., Inc. v. Exela Pharma Scis., LLC*, No. 11-733-LPS, 2013 U.S. Dist. LEXIS 166097 (D. Del. Nov. 14, 2013). For the reasons set forth *infra*, we affirm.

I. BACKGROUND

A. The Patents-In-Suit

SCR Pharmatop and Cadence Pharmaceuticals, Inc. (collectively "Cadence") are the owner and exclusive licensee, respectively, of the '222 and '218 patents. These patents are directed to aqueous phenol formulations—particularly acetaminophen (sometimes referred to as "paracetamol"). '222 patent abstract; '218 patent abstract, col.1 ll.32–33.

The '222 patent issued on February 22, 2000. It explains that in aqueous solutions, acetaminophen decomposes into potentially toxic products. *See* '222 patent col.1 ll.16–22, ll.45–48. The '222 patent is directed at avoiding this decomposition by adding a free-radical capturing

agent and a buffer. *Id.* abstract. Claim 1 of the '222 patent is the only independent claim, and recites (with the disputed term highlighted):

> 1. A stable, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium containing *a buffering agent* and at least one member of the group consisting of a free radical scavenger and a radical antagonist.

The '218 patent claims priority to a French application filed on June 6, 2000. The '218 patent discloses a method for obtaining stable acetaminophen formulations by deoxygenating solutions with an inert gas to achieve oxygen concentrations below 2 parts-per-million ("ppm"). '218 patent abstract, col.1 ll.32–33. Claim 1 of the '218 patent is the only independent claim, and recites (with the edits from the certificate of correction in brackets and the disputed terms highlighted):

> 1. A method for preparing an *aqueous solution* with an active [principle of phenolic] nature susceptible to oxidation, which is paracetamol, while preserving for a prolonged period, comprising deoxygenation of the *solution* by bubbling with at least one inert gas and/or placing under vacuum, until the oxygen content is below 2 ppm, and *optionally* the aforementioned *aqueous solution* with an active principle is *topped with an inert gas atmosphere heavier than air and placed in a closed container in which the prevailing pressure is 65,000 Pa maximum*, and the oxygen content of *the aqueous solution* is below 2 ppm, and optionally the deoxygenation of the *solution* is completed by addition of an antioxidant.

B. History of the Dispute

Cadence Pharmaceuticals Inc. markets an injectable acetaminophen product, which is approved by the Food

and Drug Administration ("FDA") and is distributed under the name Ofirmev®. The FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (better known as the "Orange Book") lists the '222 and '218 patents in connection with Ofirmev®.

Exela filed an Abbreviated New Drug Application ("ANDA") with the FDA, seeking approval of a generic equivalent of Ofirmev®. The ANDA included a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (2012) (commonly referred to as a "Paragraph IV certification") stating that the '222 and '218 patents were invalid and not infringed. In response, Cadence sued Exela for infringing claims 1, 3, 4, 5, 9, 10, 12 and 16–18 of the '222 patent and claims 1, 3, 4 and 19 of the '218 patent pursuant to 35 U.S.C. § 271(e)(2) (2012).

The district court found the '222 patent not invalid and literally infringed and the '218 patent not invalid and infringed under the doctrine of equivalents. Exela appeals both of the district court's infringement decisions and its validity decision as to the '218 patent. It does not appeal the district court's validity decision as to the '222 patent. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1) (2012).

II. DISCUSSION

A. Standard of Review

In reviewing questions of claim construction and obviousness, we review underlying factual determinations for clear error and ultimate determinations *de novo*. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015) (claim construction); *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 961 (Fed. Cir. 2014) (citing *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013)) (obviousness). Because the district court's claim constructions were based solely on the intrinsic record, the Supreme Court's recent decision in

Teva does not require us to review the district court's claim construction any differently than under the *de novo* standard we have long applied. *Fenner Invs., Ltd. v. Cellco P'ship*, --- F.3d ----, ----, *available at* 2015 WL 570730 (Fed. Cir. Feb. 12, 2015) ("When the district court reviews only evidence intrinsic to the patent . . . , the judge's determination will amount solely to a determination of law, and [we] review that construction de novo.") (quoting *Teva*, 135 S. Ct. at 841) (internal citations removed).

"Infringement, either literal or under the doctrine of equivalents, is a question of fact that we review for clear error when tried without a jury." *Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co.*, 204 F.3d 1360, 1363 (Fed. Cir. 2000) (citing *Insituform Techs., Inc. v. Cat Contracting, Inc.*, 161 F.3d 688, 692 (Fed. Cir. 1998)). "A factual finding is clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made." *Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1401, 1406 (Fed. Cir. 2014) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948) and *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006)). Whether the doctrine of equivalents would vitiate a claimed element is a question of law that we review *de novo*. *Cordis Corp. v. Bos. Scientific Corp.*, 561 F.3d 1319, 1330 (Fed. Cir. 2009) (citing *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d 1364, 1379 (Fed. Cir. 2005)).

B. The '222 Patent

1. Claim Construction

Exela's appeal regarding the '222 patent turns on claim construction. "Claim terms are generally given their plain and ordinary meanings to one of skill in the art when read in the context of the specification and prosecution history." *Golden Bridge Tech., Inc. v. Apple Inc.*, 758 F.3d 1362, 1365 (Fed. Cir. 2014) (citing *Phillips*

v. AWH Corp., 415 F.3d 1303, 1315–17 (Fed. Cir. 2005) (en banc)). A patentee can act as his own lexicographer, but, to do so, "'a patentee must clearly set forth a definition of the disputed claim term other than its plain and ordinary meaning' and must 'clearly express an intent to redefine the term.'" *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014) (quoting *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012)).

The district court construed the term "buffering agent" in claim 1 to mean "[a]n agent that helps the formulation resist change in pH." *Cadence*, 886 F. Supp. 2d at 456. The court refused to construe the term to require, as Exela urged, that the buffering agent be present "in an effective concentration to resist material changes in pH," because "nothing in the patent limits the scope of the claimed buffering agent to an 'effective concentration' or one that resists 'material changes in pH.'" *Id.*[1]

On appeal, Exela continues to urge that a "buffering agent must be present in a sufficient concentration to prevent a material change in pH." Op. Br. at 60. In support, it points to embodiments described in the specification and cites applicants' statements in the prosecution history. Cadence disputes Exela's arguments and responds that the plain and ordinary meaning of "buffering agent" does not include specific efficacy and concentration limitations.

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[1] Exela also asserted that a "buffering agent" is limited to "a weak acid and its conjugate base[] or a weak base and its conjugate acid." *See Cadence*, 886 F. Supp. 2d at 456. It does not appeal the district court's rejection of this aspect of its proposed construction.

We agree with the district court that the plain and ordinary meaning of "buffering agent" is "an agent that helps the formulation resist change in pH." We see nothing in the intrinsic record to warrant adding requirements of effective concentration or resistance to material change. The statement in the specification that the concentration of the buffer "may be" between 0.1 and 10 mg/ml is not limiting, because even if "all of the embodiments discussed in the patent" included a specific limitation, it would not be "proper to import from the patent's written description limitations that are not found in the claims themselves." *Flo Healthcare Solutions, LLC v. Kappos*, 697 F.3d 1367, 1375 (Fed. Cir. 2012) (citing *Silicon Graphics, Inc. v. ATI Techs., Inc.*, 607 F.3d 784, 792 (Fed. Cir. 2010)). Moreover, the fact that during prosecution applicants added the term "buffering agent" in response to a rejection does not show that the phrase requires a minimum concentration or resistance to material change. The addition of that phrase shows only that a buffering agent is necessary.

For the foregoing reasons, we conclude that the district court correctly construed the term "buffering agent" simply as "an agent that helps the formulation resist change in pH."

2. Infringement

Exela's appeal of the district court's finding of infringement of the '222 patent is based on its proposed claim construction, which we have now rejected. Because the district court's finding that the sodium ascorbate present in Exela's formulation as an antioxidant met the buffering agent limitation, as correctly construed, we affirm the district court's finding that claim 1 is infringed. As Exela does not assert independent non-infringement bases for dependent claims 3–5, 9, 10, 12 and 16–18, we also affirm the district court's finding of infringement of these claims.

C. The '218 Patent

Exela argues first that the district court erred in holding that Exela's process infringed the asserted claims of the '218 patent under the doctrine of equivalents, contending that reducing the amount of dissolved oxygen to below 2 ppm before acetaminophen is added is substantially different from reducing the dissolved oxygen content after acetaminophen is added. Exela next argues that the district court erred in finding infringement based on its construction of the so-called "vacuum stoppering step" of claim 1 as being merely optional. Finally, Exela challenges the district court's finding that Exela failed to show by clear and convincing evidence that the asserted claims of the '218 patent were obvious. We address each of these arguments in turn.

1. Infringement Under the Doctrine of Equivalents

The district court construed the terms "aqueous solution" and "solution" in claim 1 of the '218 patent as "[a] composition containing water as a solvent and an active ingredient susceptible to oxidation." *Cadence*, 886 F. Supp. 2d at 459. The district court thus concluded that the claimed step of "deoxygenation of the solution" required that an active ingredient already be dissolved. In other words, the district court interpreted the claim to directly cover only the method of first dissolving an active ingredient to form a solution and then deoxygenating the solution. Exela's accused process, by contrast, first deoxygenates a solvent and only then adds an active ingredient. Accordingly, the district court found that Exela did not literally infringe claim 1. *See Cadence*, 2013 U.S. Dist. LEXIS 166097, at *63–64.

Nevertheless, the district court found that Exela's ANDA formulation infringed claim 1 under the doctrine of equivalents. *See id.* at *64. It found that the timing of the addition of the active ingredient did not matter and

ruled that the differences between the claimed steps and Exela's method were insubstantial. *See id.* at *64–66.

Exela argues that the district court clearly erred in finding that there was no substantial difference between deoxygenating before or after forming the solution. Exela contends that Cadence's expert's testimony on this point was conclusory and improperly compared Exela's process, which did not involve stoppering under vacuum, with a process that did. Cadence disputes that there was clear error and contends that its expert's testimony supports the district court's decision as does the fact that Exela's formulation achieves similar stability to the formulation described in the '218 patent.

We agree with Cadence and find no clear error in the district court's finding of infringement under the doctrine of equivalents. The district court relied on the testimony of Cadence's expert, Dr. Orr, "that adding acetaminophen before or after the deoxygenation step would have no impact on the stability of the final product." *Id.* at *65. Dr. Orr explained that this was so because "in both cases you're trying to deoxygenate your solution. In both cases, you're employing bubbling to do that. And the results that you achieve under this prolonged period of—of bubbling is still a solution of less than two parts per million." This testimony supports the district court's finding that changing the timing of the deoxygenation step was an insubstantial difference. The correctness of this conclusion is confirmed by the district court's finding and Exela's accession that its formulation is, in fact, stable. *See id.* Exela's speculation that other differences between its formulation and the claimed formulation may be responsible for stability is insufficient to create a definite and firm conviction that the district court made a mistake.

The district court also did not accept Exela's argument that this scope of equivalents would vitiate a limitation of the claim. *See Cadence*, 2013 U.S. Dist. LEXIS

166097, at *66–67. Exela challenges that determination and contends that deoxygenating after adding the active ingredient is the "antithesis" of deoxygenating before adding the active ingredient and that because such a substitution would "vitiate" the claimed limitation, there can be no finding of equivalence. It maintains that the facts here are analogous to *Planet Bingo, LLC v. GameTech International, Inc.*, where we held that determining a winning combination after a game started could not be equivalent to a claim that recited "a predetermined winning combination." 472 F.3d 1338, 1345 (Fed. Cir. 2006). Cadence responds that deoxygenating prior to adding the active ingredient is insubstantially different from deoxygenating after and that reference to "vitiation" is inappropriate. According to Cadence, the finding of vitiation in *Planet Bingo* was premised on the fact that the difference in timing was substantial.

Exela's reliance on *Planet Bingo* is misplaced. *Planet Bingo*'s holding was based on a finding that a combination determined before a game was substantially different, factually, from a combination determined after the game started. *See Brilliant Instruments, Inc. v. GuideTech, LLC*, 707 F.3d 1342, 1347 (Fed. Cir. 2013) (explaining the rationale for *Planet Bingo* as "two elements likely are not insubstantially different when they are polar opposites"); *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1356 (Fed. Cir. 2012) (same). Exela's understanding of *Planet Bingo* (Fed. Cir. Dec. 13, 2006) is also expressly at odds with this court's holding in *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005 (Fed. Cir. Nov. 20, 2006), decided just a few weeks before *Planet Bingo*. *DePuy Spine* explained:

> A holding that the doctrine of equivalents cannot be applied to an accused device because it "vitiates" a claim limitation is nothing more than a conclusion that the evidence is such that no reasonable jury could conclude that an element of an

> accused device is equivalent to an element called for in the claim, or that the theory of equivalence to support the conclusion of infringement otherwise lacks legal sufficiency.

469 F.3d at 1018–19, *cited with approval* in *Voda v. Cordis Corp.*, 536 F.3d 1311, 1325 n.5 (Fed. Cir. 2008); *U.S. Philips Corp. v. Iwasaki Elec. Co. Ltd.*, 505 F.3d 1371, 1378–79 (Fed. Cir. 2007) *and Abbott Labs. v. Andrx Pharm., Inc.*, 473 F.3d 1196, 1212 (Fed. Cir. 2007).

Exela fundamentally misunderstands the doctrine of claim vitiation. "Vitiation" is not an exception or threshold determination that forecloses resort to the doctrine of equivalents, but is instead a legal conclusion of a lack of equivalence based on the evidence presented and the theory of equivalence asserted. We have repeatedly reaffirmed this proposition. *See VirnetX, Inc. v. Cisco Sys., Inc.*, 767 F.3d 1308, 1323 (Fed. Cir. 2014); *Ring & Pinion Serv. Inc. v. ARB Corp. Ltd.*, 743 F.3d 831, 836 (Fed. Cir. 2014); *Charles Mach. Works, Inc. v. Vermeer Mfg. Co.*, 723 F.3d 1376, 1380 (Fed. Cir. 2013); *Brilliant Instruments*, 707 F.3d at 1347; *Bush Hog*, 703 F.3d at 1356; *Voda*, 536 F.3d at 1325 n.5; *U.S. Philips Corp.*, 505 F.3d at 1378–79; *Abbott Labs*, 473 F.3d at 1212; *DePuy Spine*, 469 F.3d at 1018–19. Characterizing an element of an accused product as the "antithesis" of a claimed element is also a conclusion that should not be used to overlook the factual analysis required to establish whether the differences between a claimed limitation and an accused structure or step are substantial *vel non*. The determination of equivalence depends not on labels like "vitiation" and "antithesis" but on the proper assessment of the language of the claimed limitation and the substantiality of whatever relevant differences may exist in the accused structure. *See Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 610–12 (1950) (finding that a welding process that used manganese, a non-alkaline metal, could be equivalent to the claimed "alkaline earth

metal," even though an alkaline metal can formally be described as the "antithesis" of a non-alkaline metal). *But see Moore U.S.A., Inc. v. Standard Register Co.*, 229 F.3d 1091, 1106 (Fed. Cir. 2000) ("it would defy logic to conclude that a minority—the very antithesis of a majority—could be insubstantially different from a claim limitation requiring a majority, and no reasonable juror could find otherwise").

Since a reasonable trier of fact could (and, in fact, did) conclude that Exela's process is insubstantially different from that recited in the claims, the argument that a claim limitation is vitiated by the district court's application of the doctrine of equivalents is both incorrect and inapt. Therefore, we affirm the district court's determination of infringement of claim 1. Because Exela does not assert any independent bases for not infringing dependent claims 3, 4 and 19, the district court's finding of infringement of these claims is also affirmed.

2. Claim Construction of the Vacuum Stoppering Step

The district court concluded that the phrase "optionally topped with an inert gas . . . and placed in a closed container in which the prevailing pressure is 65,000 Pa maximum" (the "vacuum stoppering step") indicates that the vacuum stoppering step is optional, because "[t]he language of claim 1 plainly indicates that the word 'optionally' applies to both the first and second clauses, which are connected by the word 'and.'" *Cadence*, 886 F. Supp. 2d at 464. According to the district court, whatever statements were made during prosecution "do not rise to the level of an explicit disclaimer." *Id.* at 464–65.

On appeal, Exela contends that the vacuum stoppering step is mandatory, relying on the language of the claim, the specification and the prosecution history. Cadence responds that the plain language of the claim unambiguously recites that the vacuum stoppering step is optional and that Exela waived any argument to the

contrary. Cadence also argues that the prosecution history does not contain a clear and unmistakable disavowal of claim scope.

We conclude, as did the district court, that the step of stoppering under vacuum is optional. The plain and ordinary meaning of "optionally . . . topped . . . and placed" is that both the topping and placing steps are optional. Indeed, defendants appear to have originally conceded this point. *See* J.A. 10379 (counsel for defendants stating: "defendants' position is that the vacuum limitation is not optional, notwithstanding that it follows the 'and optionally' language phrase. I understand English language construction. And if it weren't for the prosecution history, we wouldn't be making this argument.").

The conclusion that vacuum stoppering is optional is supported by the specification, which does not describe vacuum stoppering as one of "the four parameters that have to be taken into consideration as essential for preservation." '218 patent col.6 ll.29–30. Indeed, the specification contains examples that exhibit prolonged stability even without vacuum stoppering. *Id.* col.7 ll.1-18. While some examples may work better than others, the specification's observation that stoppering under vacuum "constitutes a distinct advantage," *id.* col.5 ll.9–10, cannot be read to imply that the invention is limited to such embodiments. *Cf. Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1350 (Fed. Cir. 2013) ("'The patentee is entitled to the full scope of his claims, and we will not limit him to his preferred embodiment or import a limitation from the specification into the claims.'") (quoting *Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1348 (Fed. Cir. 2009)).

As for the prosecution history, the district court found insufficient reason to depart from the unambiguous plain and ordinary meaning of the claims themselves in reciting

the vacuum stoppering step as optional. We agree. We are not persuaded that the portions of the prosecution history cited by Exela amount to a clear and unmistakable disavowal of the unambiguous recitation of the vacuum stoppering step as being optional. Exela contends that the vacuum stoppering step is mandatory, not optional, because applicants argued that step in distinguishing the prior art during prosecution. While the vacuum stoppering step was mentioned in applicants' argument, the only factor in the reference that applicants noted in comparing the reference to the claims was the degree to which the level of oxygen was reduced. Specifically, applicants described the oxygen level of the reference by noting that "[t]he residual oxygen concentration present in the solution after bubbling of the nitrogen is *on the order of 2 ppm* . . . and this is not a satisfactory order." U.S. Pat. App. No. 10/332,060 Remarks of Mar. 18, 2005, at 8 (emphasis added). Applicants then argued that "[i]n contrast thereto, Applicants' bubbling with nitrogen is reduced to *below* 2 ppm." *Id.* (emphasis added). Granted that applicants also noted the vacuum stoppering step as a factor in providing a stable solution, but there is no clear indication that the vacuum stoppering step was the "contrast" that applicants were trying to make over the cited reference. And certainly no indication that the vacuum stoppering step should be understood as "mandatory," despite the clear language of the claim. At bottom, the language of claim 1 is unambiguous that the vacuum stoppering step is optional, and the prosecution history does not reflect a clear and unmistakable disavowal of the plain and ordinary meaning of that language.

Accordingly, we conclude that in claim 1 of the '218 patent, the vacuum stoppering step is optional and not mandatory. We thus affirm the district court's finding of infringement and need not address Cadence's alternate ground for affirmance based on its asserted construction of the term "aqueous solution."

3. Obviousness

A patent is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (2006).[2] Obviousness is a question of law, based on underlying factual determinations including: "the scope and content of the prior art"; "differences between the prior art and the claims at issue"; "the level of ordinary skill in the pertinent art"; and "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

At the district court, Exela contended that the '218 patent was obvious over the '222 patent in view of A. Palmieri, *Effect of Dissolved Oxygen Levels on Oxidative Degradation of Pyrogallol*, 67 J. Pharm. Sci. 1338 (Sept. 1978) (the "Palmieri article"). Exela claimed, and Cadence did not dispute, that the only difference between the asserted claims of the '218 patent and the disclosure of the '222 patent is that the '222 patent did not disclose decreasing the oxygen content to below 2 ppm (as recited in claim 1) or even lower levels (as recited in certain dependent claims). *Cadence*, 2013 U.S. Dist. LEXIS 166097, at *99–100, 101 n.30. Exela argued that deoxygenating below 2 ppm would have been obvious based on the disclosure of the '222 patent that the stability of acetaminophen solutions depends, *inter alia*, on "removal of oxygen dissolved in the carrier," '222 patent col.2 ll.33–

[2] Because the application that led to the '218 patent was filed prior to March 16, 2013, the America Invents Act's ("AIA") amendments to § 103 do not apply. *See* § 3(n)(1) of the AIA, Pub. L. No. 112-29.

34, and the teaching of the Palmieri article that deoxygenating pyrogallol solutions to below 0.05 ppm leads to increased stability.

The district court found that it would not have been obvious to combine the Palmieri article with the '222 patent, because pyrogallol degrades by oxidation while acetaminophen degrades primarily by hydrolysis and because deoxygenation to levels below 2 ppm was "technical[ly] difficult[]." *Id.* at *105. The district court also addressed secondary considerations, which it found to support a conclusion of non-obviousness. *See id.* at *111. According to the district court, Ofirmev®—which the district court found to be made by a process equivalent to that claimed in the '218 patent—fulfilled a long-felt need, was a commercial success, was licensed and was praised in the industry. *See id.* at *92–99. The court also found that the '218 patent exhibited unexpected results as to stability as compared to the '222 patent. *See id.* at *109–11.

On appeal, Exela argues that the district court committed clear error in failing to recognize that the '222 patent's Example II suggests that hydrolysis is not the primary degradation pathway and in failing to recognize that the Palmieri article teaches the importance of reducing dissolved oxygen to trace levels. Exela also contends that the district court's findings as to secondary considerations relating to Cadence's distribution of Ofirmev® are not probative of non-obviousness because the claims of the '218 patent recite deoxygenating *after* the addition of an active ingredient whereas in Ofirmev® the solvent is deoxygenated *before*. It also claims that any secondary considerations lack a nexus to the novel features of the '218 patent. Finally, it contends that the unexpected results are only a matter of degree.

Cadence responds that the Palmieri article is inapposite as it deals with compounds that degrade via a differ-

ent mechanism and that Exela failed to prove that skilled practitioners would have been motivated to combine the '222 patent with the Palmieri article. According to Cadence, the secondary considerations further support a finding of non-obviousness.

Exela bears a difficult burden in this case on the question of obviousness. First, since the Examiner initially rejected the claims of the '218 patent for essentially the same reasons as defendants now raise, *see Cadence*, 2013 U.S. Dist. LEXIS 166097, at *100 n.29 (quoting the Examiner's Reasons for Allowance), the Patent Office is "'presumed to have properly done its job'" when it ultimately allowed the '218 patent. *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed. Cir. 1984)). Second, patents are presumed to be valid, 35 U.S.C. § 282, so defendants must prove invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011). Third, we will only overturn the district court's underlying factual determinations if we believe they are clearly erroneous.

Exela has not met its burden. The district court found the teachings of the '222 patent and the cited Palmieri article lacking, as do we. The district court found that skilled artisans understood acetaminophen to be primarily degraded via *hydrolysis*. *Cadence*, 2013 U.S. Dist. LEXIS 166097, at *104 (crediting Kenneth A. Connors et al., *Chemical Stability of Pharmaceuticals* 18–19 (1979) and the testimony of Dr. Elder). Exela argues that the district court was wrong in failing to appreciate that the '222 patent discloses that acetaminophen is in fact subject to oxidation, followed by hydrolysis. It points specifically to the hypothesis in the '222 patent specification that: ". . . in contrast to what has been reported in the literature, the breakdown of acetaminophen first involves

an ox[i]dative process followed by hydrolysis," '222 patent col.10 ll.41–45.

The district court correctly rejected Exela's argument. At trial, one of the inventors, Francois Dietlin, in discussing Example II, testified that the experiments he performed confirmed that degradation of acetaminophen resulted from hydrolysis, followed thereafter by oxidation. Moreover, Cadence's expert, Dr. Edmond Elder, testified that the *primary* degradation mechanism in acetaminophen is hydrolysis. This is consistent with the discussion of the prior art in the '222 patent that notes the reason "paracetamol in aqueous solution is unstable [is] primarily correlate[d] with hydrolysis." *Id.* at col.1 ll.30–31. Finally, we note that Dr. Palmieri, testifying as Exela's expert, admitted that deoxygenation would not be effective to prevent *hydrolytic* degradation. *See Cadence*, 2013 U.S. Dist. LEXIS 166097, at *104.

The district court thus was correct in concluding that it would not have been obvious to combine the Palmieri article with the '222 patent, because the Palmieri article addressed the degradation of pyrogallol—which degrades primarily by oxidation—and did not address the degradation of acetaminophen—which, as noted above—degrades primarily by hydrolysis. At bottom, we agree with the district court that Exela has not proven by clear and convincing evidence that a person of ordinary skill in the art would have attempted to deoxygenate an acetaminophen solution to below 2 ppm with a reasonable expectation of "preserving [the acetaminophen] for a prolonged period," as recited in claim 1.

Regarding secondary considerations, we agree with the district court that secondary considerations related to the marketing of Ofirmev® are not per se irrelevant to the non-obviousness of the claims of the '218 patent, despite the fact that the claims do not literally cover Ofirmev®. As discussed above, *supra* at p. 9, whether a solvent is

deoxygenated before or after the active ingredient has been dissolved is an insubstantial difference. Thus, there is no reason to believe that any secondary considerations attendant to Ofirmev®, in which the solvent is deoxygenated prior to the addition of the active ingredient, would not also be present in formulations literally covered by the claims, i.e., where the solvent is deoxygenated after the addition of active ingredient.

The district court also did not clearly err in finding that the process claimed in the '218 patent achieved unexpected stability relative to that disclosed in the '222 patent and in finding that the licensing of the '218 patent is probative of non-obviousness. Formulations made pursuant to the methods described in the '218 patent were stable for two years, '218 patent col.8 ll.11–17, whereas plaintiff's expert testified that the formulation taught in the '222 patent only achieved several months' stability. Even if these results were only somewhat unexpected, they are still evidence of non-obviousness, albeit less so than if the results were vastly unexpected. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (citing cases). That the '218 patent was separately licensed, *see Cadence*, 2013 U.S. Dist. LEXIS 166097, at *5–6, is also evidence of a belief that the '218 patent was valid.

Based on the foregoing, we conclude that Exela has not proven that the asserted claims of the '218 patent are obvious.

III. CONCLUSION

For the foregoing reasons, we affirm the district court's determination that the '222 and '218 patents are infringed and its determination that the '218 patent has not been shown to be invalid.

AFFIRMED