Nos. 17-1153, 17-2048, 17-2049, 17-2050

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

GRÜNENTHAL GMBH, DEPOMED, INC.,
Plaintiffs-Cross-Appellants,

v.

ALKEM LABORATORIES LIMITED, WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED, WEST-WARD PHARMACEUTICALS CORP.,
Defendants-Appellants,

ACTAVIS ELIZABETH LLC,
Defendant-Appellee,

ACTAVIS LABORATORIES UT, INC.,
Defendant.

On Appeal From the United States District Court for the District of New Jersey in Case Nos. 2:13-cv-04507-CCC-MF, 2:13-cv-06929-CCC-MF, 2:13-cv-07803-CCC-MF, 2:14-cv-03941-CCC-MF, 2:14-cv-04617-CCC-MF, 2:15-cv-06797-CCC-MF, Judge Claire C. Cecchi

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PRINCIPAL AND RESPONSE BRIEF FOR CROSS-APPELLANT DEPOMED, INC.

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FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Grunenthal GmbH **v.** Alkem Laboratories Ltd.

Case No. 17-1153, 17-2048, 17-2049, 17-2050

CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ■ (appellant) ☐ (respondent) ☐ (appellee) ☐ (amicus) ☐ (name of party)

cross-

Depomed, Inc.

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Depomed, Inc.	None	BlackRock, Inc.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court **(and who have not or will not enter an appearance in this case)** are:

Gibson, Dunn & Crutcher LLP: Frank P. Cote, David Glandorf, Theodore Kwong
Robinson Miller LLC: Donald A. Robinson, Keith J. Miller
Sidley Austin LLP: David A. Pritikin, William H. Baumgartner, Steven J. Horowitz, Jessica A. Johnson, Rachel H. Townsend, Bindu Donovan, Isaac Olson

FORM 9. Certificate of Interest **Form 9**
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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

None

12/1/2017
Date

/s/ Michael A. Sitzman
Signature of counsel

Please Note: All questions must be answered

Michael A. Sitzman
Printed name of counsel

cc: All counsel of record via CM/ECF

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for cross-appellant Depomed, Inc. states that no appeal in or from this same proceeding was previously before this Court or any other court.

INTRODUCTION

In 2008, the Food and Drug Administration ("FDA") approved NUCYNTA® ER (tapentadol) for the treatment of polyneuropathic pain. It was the first and only opioid medication approved specifically for the treatment of polyneuropathic pain, including polyneuropathic pain associated with the devastating condition of diabetic peripheral neuropathy. Ten years later, with millions of patients successfully treated, NUCYNTA® ER remains the only opioid medication approved for the treatment of polyneuropathic pain.

In this litigation, Defendants West-Ward Pharmaceuticals International Ltd. and West-Ward Pharmaceuticals Corp. (together "West-Ward"), Alkem Laboratories Ltd., and Actavis Elizabeth LLC (collectively, "Defendants") filed Abbreviated New Drug Applications ("ANDAs") seeking regulatory approval of generic versions of NUCYNTA® ER. Each defendant challenged the validity and infringement of Depomed, Inc.'s and Grünenthal GmbH's (collectively, "Plaintiffs") U.S. Patent No. 8,536,130 (the "'130 patent"), which claims a method for treating polyneuropathic pain with tapentadol hydrochloride. After a bench trial, the district court correctly assessed the evidence in holding that the asserted claims of the '130 patent are not invalid. The court, however, committed several legal and factual

errors in finding no induced or contributory infringement by West-Ward and Actavis, despite undisputed evidence to the contrary.[1]

Accordingly, this Court should affirm the district court's holding that the asserted claims of the '130 patent are not invalid, and reverse the court's conclusion of no induced or contributory infringement.

COUNTERSTATEMENT OF JURISDICTION

Depomed agrees with West-Ward's jurisdictional statement, but adds that this Court has jurisdiction over Plaintiffs' cross-appeal under 28 U.S.C. § 1295(a).[2]

COUNTERSTATEMENT OF THE ISSUES

I. West-Ward's and Alkem's Appeal

Whether the district court correctly held that Defendants failed to prove by clear and convincing evidence that claims 1, 2, 3, and 6 of the '130 patent are invalid as anticipated or for obviousness-type double patenting.

II. Plaintiffs' Cross-Appeal

1. Whether the district court erred in concluding that Actavis and West-Ward would not induce infringement of the asserted claims of the '130 patent that

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[1] Alkem was found to induce infringement of the '130 patent, and has chosen not to appeal from that portion of the decision.

[2] The district court entered judgment pursuant to Federal Rule of Civil Procedure 54(b) as there remains a pending and stayed claim for infringement of U.S. Patent No. 8,309,060.

recite a method of treating polyneuropathic pain, even though the experts all agreed that the indication in the generic product labels by definition includes polyneuropathic pain.

2. Whether the district court erred in concluding that Actavis and West-Ward would not contributorily infringe the asserted claims of the '130 patent on the sole basis that there would be some noninfringing uses of their generic products despite unrefuted evidence that the frequency of such uses would be rare.

COUNTERSTATEMENT OF THE CASE

I. Background: Grünenthal's Discovery of Tapentadol

A. The Search for a New Opioid

In the early 1960s, Grünenthal identified and developed a new opioid medication for treating moderate pain called tramadol, which is a centrally acting analgesic. *See* Appx8310 (10:4-6); Appx46497-46528 at Appx46500; Appx45910-45940 at Appx45913. Tramadol was quite successful and gained widespread approval and use in Europe and the United States. Despite its success, tramadol was considered a weak opioid with complex active, non-opioid metabolites, and its active form was a racemic mixture of R and S enantiomers. Given tramadol's various shortcomings, by the late 1980s Grünenthal began searching for a "tramadol successor." Appx8311 (11:9-21); Appx46497-46528 at Appx46509; Appx46529-46622 at Appx46529.

After ten years of searching and analyzing over 500 compounds, Grünenthal saw "no real prospect of success." Appx45944-45947 at Appx45944; Appx46497-46528 at Appx46509; Appx83190-8320 (19:23-21:5). In 1992, as part of these efforts, Grünenthal hired Dr. Helmut Buschmann to head up one of its laboratories. Appx46397-46528 at Appx45910-45940, Appx45917, Appx46504; Appx8308-8309 (8:4-9:8); Appx8310-8311 (10:7-11:8); Appx8312 (12:8-13); Appx46040-46041. By then, Grünenthal had examined over 800 different compounds. Appx8349-8352 (49:12-52:23); Appx46529-46622 at Appx46531-46532, Appx46569.

Dr. Buschmann took Grünenthal in a completely different direction, jettisoning the fundamental teachings of tramadol. One of the most controversial steps he took was to open up the cyclohexane ring, which was the hallmark of tramadol, and to begin synthesizing linear molecules. Appx8319-8326 (19:23-21:5, 21:8-24:20, 24:24-26:3); Appx8328-8329 (28:20-29:5); Appx8380 (80:11-81:6). Despite criticism and skepticism by everyone else at Grünenthal, Dr. Buschmann's linear compounds were tested and each was found to have clear analgesic activity. Appx10900 (23:9-18); Appx11264 (115:18-25); Appx44310-44357 at Appx44351; Appx44358-44404 at Appx44399; Appx46042-46056 at Appx46055; Appx44405-44431 at Appx44418.

On January 26, 1994, after Dr. Buschmann synthesized over 300 different compounds, he finally synthesized what is now known as tapentadol. Appx45469-45902 at Appx45564; Appx8321-8322 (21:13-22:16); Appx8326-8327 (26:4-27:19); Appx45083-45468; Appx45469-45902 at Appx45564; Appx44432-45082 at Appx44578.

B. Clinical Trials

Beginning in late February 1994, Grünenthal obtained isolated animal test data for tapentadol along with other linear compounds produced by Dr. Buschmann. Appx8345-8349 (45:8-49:11); Appx46101-46496 at Appx46301-46303, Appx46307, Appx46312. The data was from a mouse writhing test, which is well-known to be a test for purely nociceptive pain, a specific type of pain discussed further below. Appx11268-11269 (119:9-120:1); Appx9320 (299:4-7); Appx9330-9331 (309:19-310:4); Appx50553-50584 at Appx50570. The mouse writhing test was the common "industry standard" by which most analgesics were analyzed in drug development. Appx11268-11269 (119:9-120:1).

Positive animal results for tapentadol led to its selection as the lead drug candidate for larger-scale clinical trials, which ultimately supported the marketing approval for tapentadol. Appx8379 (79:11-24). In September 2014, the International Union of Pure and Applied Chemistry (IUPAC) awarded Dr. Buschmann the IUPAC-Richter Prize "in recognition of his outstanding creative

contributions to the invention, discovery, and development of the novel analgesic drug tapentadol." Appx8384-8385 (84:25-85:20); Appx46040-46041.

C. The '593 Patent

To protect the novel class of linear compounds that Dr. Buschmann discovered, Grünenthal filed for patent protection and obtained U.S. Patent No. 6,248,737 (the "'737 patent"). Appx44405-44431. U.S. Patent No. RE39,593 (the "'593 patent") is a reissue of the '737 patent, which has an effective filing date of July 23, 1994, and issued on June 19, 2001. Appx7787 ¶ 26. The only analgesic data disclosed in the '737 patent (and the '593 patent) is from the purely nociceptive pain model described above—the mouse writhing test. Appx385-386 ('593 patent, 22:53-23:47); Appx451 ('593 patent, 21:54-22:47).

Following a bench trial, the district court in this case held that each of the Defendants infringe the asserted claims of the '593 patent, and that the claims are not invalid. Appx38; Appx93-127. Defendants have not appealed from that determination.

II. Understanding Pain and Analgesics

Before proceeding to the '130 patent and the related issues on appeal, it is important to provide the Court with some background and context to the practice of pain management and the use of analgesics.

The word "pain" refers not to an actual cause of pain, but rather a symptom: an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Appx52823-52829 at Appx52823; Appx9386 (38:4-15). Different terms are used to refer to different symptoms versus different types of pain:

Symptom—Acute vs. Chronic Pain (Length of Time). Acute pain is pain generally lasting between approximately three to six months, and is expected to heal over time. Appx9387-9388 (39:25-40:3). On the other hand, chronic pain is pain that generally lasts longer than six months and is not expected to heal. *Id.* (40:4-7).

Symptom—Mild, Moderate and Severe Pain (Intensity). Severe pain refers to the intensity of pain, which can be measured in terms of grades, such as mild, moderate, or severe—with severe pain being the most intense. Appx9389 (41:15-18).

Types—Nociceptive vs. Neuropathic Pain. The types of pain relevant to this appeal fall into two categories: nociceptive and neuropathic (including polyneuropathic) pain.

Nociceptive pain is pain caused by actual or threatened damage to *non*-nerve tissue and is due to the activation of sensory receptors from, for instance, a noxious stimulus. Appx52823-52829 at Appx52827; Appx9188-9189 (167:24-168:16); Appx9386-9387 (38:23-39:1). A patient typically describes nociceptive pain as a

throbbing or aching pain, such as a toothache or the pain one feels when hitting his thumb with a hammer. Appx9386-9387 (38:23-39:1); *see also* Appx9189 (168:6-16); Appx10611 (35:4-9). Nociceptive pain is "expect[ed] . . . to heal," and thus nociceptive pain is "most often acute" rather than chronic, and is "typically . . . not treated with around the clock [medication]"—instead, nociceptive pain is generally treated "more with an as needed medication." Appx9388-9389 (40:15-41:8); Appx9472 (62:5-9); Appx9457 (47:9-14). Nociceptive pain can also be severe, but the severity of the pain does not change the type of pain being experienced. Appx9389 (41:19-21).

Neuropathic pain is separate and distinct from nociceptive pain, and patients often describe the two types very differently. Appx9387 (39:9-10); Appx11266-11267 (117:21-118:23); Appx9189-9190 (168:17-169:1). Neuropathic pain is pain caused by a lesion or disease of the somatosensory nervous system, and therefore involves actual damage to nerves, *i.e.*, a spinal cord injury. Appx52823-52829 at Appx52826; Appx9189-9190 (168:17-169:1); Appx9387 (39:6-9). Because it is difficult for damaged nerves to regenerate, neuropathic pain is most often chronic and "is very difficult to treat." Appx9388-9389 (40:15-41:13); Appx10675 (99:8-16); Appx10617 (41:9-11); Appx9191 (170:3-4). Thus, unlike nociceptive pain, neuropathic pain often requires "around-the-clock" treatment. *Id.* Finally, neuropathic pain is most often severe. Appx9389 (41:19-23); Appx10675 (99:8-

16); Appx10617 (41:9-11); Appx9247-9248 (226:23-227:8); Appx9207 (186:21-23).

Polyneuropathic pain refers to neuropathic pain caused by damage to *multiple* nerves. Appx10610 (34:2-5). There are many types of polyneuropathic pain, one of which is diabetic peripheral neuropathy ("DPN"). Appx9387 (39:6-15). **Mononeuropathic pain** refers to neuropathic pain caused by damage to a single nerve. Appx10610 (34:6-7); *see also* Appx9460 (50:10-13). Because the pain originates in a single nerve, mononeuropathic pain is quite rare. *See* Appx9471-9472 (61:22-62:12); Appx9486 (76:14-23).

The Treatment of Pain. Just as nociceptive pain and neuropathic pain are separate and distinct, the treatment of one is not predictive of the other. Appx9387 (39:9-10); Appx11266-11267 (117:21-118:23); Appx11161-11162 (12:25-13:21); Appx11180 (31:9-13); Appx11187-11188 (38:21-39:15); Appx11219 (70:20-22); Appx10609-10611 (33:6-35:9); Appx10704 (128:6-8); Appx9188-9189 (167:21-168:5); Appx9189-9190 (168:17-169:8); Appx9191 (170:1-7). In fact, for the reasons discussed above, neuropathic pain "is very difficult to treat" in comparison to nociceptive pain. Appx9389 (41:9-13).

Analgesics like tapentadol are compounds that can treat pain by affecting the nerve receptors in the human body that are associated with communicating pain from the site of injury to the brain, and molecules that bind to those receptors. Appx48;

Appx10954 (77:13-16). Analgesics can be agonists, antagonists, or—like tapentadol—have both types of activity. Appx10964-10965 (87:16-88:2). An agonist, such as an opioid, "kicks the receptor into high gear," whereas an antagonist "shuts the receptor off." Appx10964-10965 (87:16-88:2).

The Controversy in Using Opioids to Treat Polyneuropathic Pain. The treatment of pain "involves many considerations other than simply identifying a drug that exhibits efficacy in lowering a patient's pain score," such as a patient's quality of life and how side effects affect the patient. Appx187; Appx11173 (24:2-11); Appx10671 (95:15-23). Opioids have been known to treat purely nociceptive pain, as their mechanism of action is to attach to opioid receptors in the body that cut off pain signals from the site of an injury to the brain (the nociceptive pathway). But before 2007, and continuing even today, there was widespread controversy surrounding the use and efficacy of opioids in treating neuropathic pain. Because neuropathic pain requires "around-the-clock" pain management, using opioids often leads to severe side effects, limited effectiveness, and other serious risks to a patient's quality of life. Appx188; Appx58359-58387; Appx58437-58451; Appx58529-58536; Appx58537-58546; Appx58547-58598; Appx58518-58528.

Thus, as of 2007, the "standard was not to prescribe opioids for neuropathic pain," for several reasons. Appx11163 (14:5-8). For instance, opioids can cause severe side effects, including "constipation, nausea, vomiting, sleepiness, [and]

dizziness." Appx11175-11176 (26:22-27:5). And patients who cannot "tolerate" the medication "because of the side effects" will often discontinue use altogether. *Id*. In addition, neuropathic pain is "refractory to opioids," meaning that opioids were ineffective or "require[d] much higher doses." Appx11163 (14:6-8); Appx11164 (15:4-8). And prescribing opioids at higher doses causes "significant issues," including hormone changes and a "dysfunction or sensitivity" of the normal nociceptive pain pathways called hyperalgesia, where a patient experiences pain "far out of category or out of relation to what" a normal individual's pain level might be. Appx11164 (15:15-25); Appx11165 (16:3-10).

III. The '130 Patent

A. The Claimed Invention: Tapentadol's Unexpected and Surprising Efficacy in Treating Polyneuropathic Pain

In light of Dr. Buschmann's development of and work on a new class of analgesics described in the '737 patent, and given the global need for a polyneuropathic pain treatment, Grünenthal decided to examine tapentadol in models of neuropathic and polyneuropathic pain. To that end, in 1996 Grünenthal hired Dr. Thomas Christoph to start a neuropathic pain department and perform neuropathic pain studies on tapentadol. Appx11702-11703 (11:10-13, 11:21-12:15); Appx11707-11708 (16:17-17:3).

In 1998 and 1999, Dr. Christoph studied tapentadol using the Bennett and Chung mouse models, which are models of mononeuropathic pain. Appx56506-

56518; Appx56519-56531; Appx11708-11714 (17:4-21:7, 21:10-23:24). The results demonstrated a dose-dependent inhibition of mononeuropathic pain by tapentadol. Appx56506-56518 at Appx56513; Appx11711 (20:15-18); Appx11714 (23:1-10); Appx56519-56531 at Appx56526. And in 2000, further tests demonstrated that, in comparison to morphine—the "gold standard" of opioid treatments for nociceptive pain—tapentadol displayed a superior tolerance profile by remaining efficacious for a longer period of time. Appx56592-56618; Appx11714-11715 (23:25-24:5, 24:11-23); Appx11717-11718 (26:28-27:24); Appx9359 (11:15-21); Appx9360 (12:14-20). The tests also demonstrated that tapentadol inhibits neuropathic pain through a mechanism of action separate and apart from its opioid receptor agonist mechanism of action. Appx56592-56618 at Appx56602; Appx11715-11716 (24:24-25:18); Appx11719-11720 (28:3-29:9); *see also* Appx56656-56673 at Appx56663-56664; Appx11746-11747 (55:9-56:7); Appx11748 (57:13-16); Appx56674-56710 at Appx56689-566990.

In view of the strong results tapentadol exhibited in these mononeuropathic models, Dr. Christoph decided to examine tapentadol in polyneuropathic pain models, but at the time Grünenthal lacked the capability. Appx11720 (29:20-22). At Dr. Christoph's suggestion, Grünenthal hired Dr. Murielle Meen to assist him in developing polyneuropathic pain models at Grünenthal. Appx11720-11721 (29:23-30:4). Dr. Christoph explained that Grünenthal needed these models to further

analyze tapentadol to see if it would satisfy the unmet need for polyneuropathic pain treatment. Appx11721 (30:5-14).

The first polyneuropathic pain model developed and used in Dr. Christoph's lab was the streptozotocin ("STZ") model. Streptozotocin induces diabetes, leading to DPN, a type of polyneuropathic pain. Appx56532-56566; Appx11720 (29:13-19); Appx11721-11722 (30:25-31:25). The evidence from the STZ model was overwhelming: tapentadol possessed a clear and significant effect in treating polyneuropathic pain. Appx56532-56566 at Appx56541; Appx11723-11724 (32:21-33:14) (tapentadol had a "clear-cut, very, very stable result, and a dose-dependent increase up to the maximal level"). The STZ experiments were completed on December 18, 2002. Appx56532-56566 at Appx56537; Appx11757 (66:19-21). Evidence from the STZ model provided a strong suggestion about "possible efficacies . . . in clinical therapy." Appx56532-56566 at Appx56544; Appx11724-11725 (33:15-34:4); *see also id.* at Appx11708 (17:9-23) ("pain wiring" in rats is very similar to that of humans). Based on the *in vivo* data, Dr. Christoph "expect[ed] a very strong effect of tapentadol in polyneuropathic pain" in humans. Appx11745 (54:13-24).

Subsequently, Dr. Christoph obtained additional evidence supporting tapentadol's ability to treat polyneuropathic pain by using the vincristine model. Appx56567-56576; Appx11725-11726 (34:8-35:1); Appx11727 (36:4-9).

Tapentadol again showed a clear and significant effect in treating polyneuropathic pain in the vincristine model. Appx56567-56576 at Appx56574; Appx11725 (35:18-24).

Dr. Christoph demonstrated that tapentadol possesses very unexpected properties in treating polyneuropathic pain. Appx56742-56846 at Appx56820-56828. First, he discovered that tapentadol unexpectedly provides the benefit of treating mononeuropathic pain and polyneuropathic pain without inhibiting normal nociceptive pain transmissions. Appx437 ('130 patent, 16:62-66) (tapentadol "produces a selective inhibition of the pathologically induced pain response, without at the same time influencing the normal pain response"); Appx56742-56846 at Appx56820-56828; Appx11728 (37:9-21); Appx11729-11731 (38:5-40:14); Appx11732-11737 (41:9-43:2, 43:24-46:22); Appx11740-11741 (49:15-50:8); Appx56619-56633. This selective inhibition of neuropathic pain without affecting nociceptive pathways is significant insofar as it allows for neuropathic pain treatment without impairing the normal, protective mechanisms of nociceptive pain. *See* Appx11266-11267 (117:21-118:23); Appx11737-11738 (46:23-47:14). Morphine could not treat mononeuropathic or polyneuropathic pain without also inhibiting the normal nociceptive pain pathway, which is a severe disadvantage in treating neuropathic pain. Appx56742-56846 at Appx56826-56827 ¶ 21 (Tab I); *id.* at Appx56827 ¶ 21 (Tab I); Appx11731 (40:2-9); Appx11733 (42:18); *see also*

Appx11164 (15:1-11). This is the primary reason why opioids were not used for the treatment of neuropathic pain.

Second, Dr. Christoph discovered that tapentadol is unexpectedly more potent in the treatment of polyneuropathic pain—the more complicated and severe pain condition—than it is for treating mononeuropathic pain. By comparing the results from Grünenthal's redesigned Chung and STZ rat models, Dr. Christoph discovered that tapentadol's ***minimal*** effective dose for treating polyneuropathic pain is three times lower than the minimal effective dose for treating mononeuropathic pain. Further, tapentadol's ***maximum*** effective dose is ten times lower for treating polyneuropathic pain than for treating mononeuropathic pain. Appx11738-11739 (47:16-48:7). These results were completely surprising since polyneuropathic pain is the more severe pain condition and yet it required a lower dose of tapentadol to provide an effective treatment and a much lower dose to see the maximum effective treatment. Appx11704 (13:12-23); Appx11739 (48:7-13).

Third, Dr. Christoph discovered that, in the treatment of polyneuropathic pain, tapentadol outperformed morphine—the "gold standard" for treating nociceptive pain. Appx56742-56846 at Appx56827; Appx9359 (11:16-21); Appx9360 (12:14-20). It was "astonishing" that less tapentadol was required to achieve the same level of efficacy as morphine. Appx11742 (51:4-25). This result was even more surprising because in other pain models, morphine is clearly more potent than

tapentadol. Appx11743-11745 (52:1-54:1). No other compounds tested by Dr. Christoph behaved like this. *Id.*

Fourth, Dr. Christoph discovered that tapentadol possesses multiple layers of synergism. For example, at trial, Dr. Christoph explained that tapentadol surprisingly possessed an "intrinsic" synergy between its multiple mechanisms of action in treating neuropathic pain. Appx11750-11753 (59:5-62:15). This was the subject of a peer-reviewed article that Dr. Christoph published in 2011. Appx56647-56655. In addition, Dr. Christoph discovered a "site-site" synergy in the spinal and supraspinal sites: administering tapentadol at these two locations results in a synergistic effect—a greater potency than expected based on the polyneuropathic pain models. Appx11751-11753 (60:18-61:3,61:13-62:1). This particular synergistic effect was "quite surprising" because this type of synergy is "relatively rare." Appx11753 (62:11-15); Appx56711-56718. These synergistic effects provide some explanation for tapentadol's unique and unexpected properties like its dose reduction ability to achieve the desired result. Appx11745 (54:7-12); Appx11750 (59:11-17); Appx11751 (60:7-17); Appx11753-11754 (62:23-63:21); Appx56647-56655.

Fifth, the data surprisingly showed that tapentadol selectively inhibits neuropathic pain over nociceptive pain. Appx428-438 ('130 patent, Table 1 ("ipsi" refers to neuropathic pain, and "contra" refers to nociceptive pain)); Appx435 ('130

patent, Table 2 ("diabetes" refers to polyneuropathic pain)); Appx56742-56846 at Appx56827; Appx11731 (40:19-25) ("[W]e don't find any—at the same dose, we don't find any strong effect [from tapentadol] on the nociceptive system"); *id.* (40:2-9) (discussing what effects that opioids would "characteristically" have on the "nociceptive" pain system); *see also* Appx56619-56633; Appx56577-56591.

The discoveries by Dr. Christoph and the other co-inventors of the '130 patent were published by Grünenthal. *See* Appx56278-56284; Appx56292-56311; Appx11764 (73:20-23); Appx11765 (74:9-22); Appx11763-11764 (72:25-73:14); Appx11767 (76:11-14); Appx11769 (78:2-9); *see also* Appx11706 (15:21-25); Appx11760-11761 (69:15-70:1); Appx56742-56846 at Appx56779-56780. The '130 patent discloses the results of Dr. Christoph's experiments discussed above, including that tapentadol hydrochloride is "surprisingly particularly effective in treating polyneuropathic pain and diabetic neuropathic pain" in comparison to, for example, mononeuropathic pain. Appx430 ('130 patent, 2:48-52); Appx434-438 ('130 patent, 10:40-17:22).

B. The Asserted Claims of the '130 Patent

Depomed has an exclusive license to Grünenthal's '130 patent. Appx8287 (186:9-22); Appx8298 (197:14-18); Appx43960-44202 at Appx43965. Plaintiffs asserted claims 1, 2, 3, and 6 of the '130 patent against Alkem, and claims 1 and 2 against Actavis and West-Ward. Appx17706-17714. All four claims recite a

method of treating polyneuropathic pain or a specific type thereof, with tapentadol. Claim 1 recites a "method of treating polyneuropathic pain in a subject suffering therefrom" by "administering to said subject an effective polyneuropathic pain inhibiting amount of" tapentadol "or a pharmaceutically acceptable salt thereof," such as tapentadol. Appx438 ('130 patent, 18:2-6). Claim 2 depends from claim 1 and recites the same method, but with administration of tapentadol specifically. *Id.* (18:8-10). Claims 3 and 6 also recite the same method, but to treat DPN specifically. *Id.* (18:11-21).

C. Induced Infringement of the '130 Patent

1. The Product Labels and the Severe Chronic Pain Indication

The NUCYNTA® ER Label. In light of its unique features, NUCYNTA® ER "was the first" and still is the *only* "opioid ever approved by the FDA for the treatment of polyneuropathic pain." Appx11175 (26:18-21); Appx10697 (121:9-12).

Original Version: The original version of the NUCYNTA® ER label contained one indication: "for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." Appx8857-8858 (17:6-18:5); Appx50310-50348 at Appx50310. FDA approved this severe chronic pain indication based on two clinical studies—one for DPN, which is a type of polyneuropathic pain, and another for

chronic lower back pain ("CLBP"), which is often polyneuropathic in nature. Appx50349-50418 at Appx50370 § 4 and Appx50373 § 4.3.1; Appx50129-50135; Appx8851 (11:8-25); Appx8852-8853 (12:22-13:8); Appx8853-8858 (13:3-18:5); Appx43889-43959 at Appx43920. These studies were included in the original label. Appx50310-50348 at Appx50310 and Appx50335-50337.

Current Version: The current version of Plaintiffs' NUCYNTA® ER label contains the severe chronic pain indication (modified according to FDA) and a specific DPN indication:

> (1) "pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate" (the "severe chronic pain indication"); and
>
> (2) "neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate" (the "DPN indication").

Appx50299-50309; Appx43889-43959 at Appx43920. FDA approved the DPN indication based on a second successfully conducted DPN study. Appx8863-8864 (23:13-24:7); Appx50136-50298; Appx43889-43959 at Appx43920.

These indications by definition instruct as to the drug's "*intended* use or uses" that FDA has "approved" to be "safe and effective." *U.S. ex. rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613, 615 (2d Cir. 2016) (citing, *e.g.*, 21 U.S.C. § 355(a), (d), and *United States v. Caronia*, 703 F.3d 149, 152-53 (2d Cir. 2012)) (emphasis added).

The label itself contains no explicit references to the word "polyneuropathic pain." Appx50299-50309.

In addition, and of relevance to this appeal, the current version of the label also contains studies on the effectiveness of the drug in treating CLBP and DPN, which studies were required for FDA approval. Appx8857-8858 (17:6-18:6); Appx8863-8864 (23:13-24:7); Appx8968-8969 (128:19-129:17); Appx50310-50348 at Appx50310 and Appx50335-50337; Appx50091-50128 at Appx50121-50123; Appx50136-50298.

Actavis's and West-Ward's Labels. Unlike Alkem,[3] Actavis and West-Ward removed the DPN indication from their proposed labels under 21 U.S.C. § 355(j)(2)(A)(viii), leaving in the severe chronic pain indication. Appx52830-53000 at Appx52876, Appx52894; Appx56114-56142 at Appx56114, Appx56133; *see also* Appx64258-64263; Appx64267; Appx64269-64270. In addition, their labels do not contain the DPN studies found in the NUCYNTA® ER label.

2. The Experts Agreed That the Severe Chronic Pain Indication Includes Polyneuropathic Pain

At trial, all the experts agreed that polyneuropathic pain is a common form of severe chronic pain and thus, that the severe chronic pain indication in Actavis's and

[3] Alkem's label is virtually identical to the NUCYNTA® ER label, and the trial court held that Alkem infringes all asserted claims of the '130 patent. Appx171-172.

West-Ward's labels includes polyneuropathic pain. Appx9388-9389 (40:18-41:13, 41:19-23); Appx9452-9453 (42:24-43:10); Appx9466-9467 (56:20-57:22); Appx9492 (82:4-9); Appx9482 (72:9-14); Appx11889 (44:15-21); Appx10617 (41:9-11); Appx10675 (99:8-16); Appx9207 (186:21-23); Appx9246 (225:22-226:8). And even though the words "polyneuropathic pain" do not explicitly appear in the labels or indication, it would be readily apparent to physicians and other prescribers (like the experts) that polyneuropathic pain is an "intended use" approved by FDA. Appx9498 (88:12-15); *Pfizer*, 822 F.3d at 615. Indeed, the "[t]arget audience" for these labels is "[p]rescribers," such as "[d]octors, nurse practitioners, [and] physicians assistants." Appx11936 (91:4-8); Appx9250 (229:15-18).

D. Contributory Infringement of the '130 Patent

The parties do not dispute that, based on the '130 patent claims and the severe chronic pain indication, a noninfringing use of Actavis's and West-Ward's products occurs when the pain treated with tapentadol is: (1) severe *and* chronic; and (2) not polyneuropathic in nature, *i.e.*, purely nociceptive pain or mononeuropathic pain.

Neither Actavis's expert nor West-Ward's expert testified as to the frequency of any alleged noninfringing uses of their products—and neither defendant provided any other evidence on frequency. Actavis's expert testified that using tapentadol to treat purely nociceptive pain or mononeuropathic pain would not be "impractical,"

"aberrant," "experimental," "far-fetched," or "illusory." Appx9226-9227 (205:12-206:21). Similarly, West-Ward's expert offered that he would use tapentadol to treat certain conditions, such as osteoarthritis and rheumatoid arthritis (RA), diabetic neuropathy, and CLBP due to purely nociceptive pain. But on cross-examination, he conceded that: (1) osteoarthritis and RA can be *acute* pain (not a noninfringing use); (2) diabetic neuropathy "generally . . . is a polyneuropathy" (is an infringing use); and (3) CLBP can be purely or partly polyneuropathic in nature (can be an infringing use). Appx10680-10681 (104:6-105:5).

Given the complete lack of evidence from Actavis and West-Ward, Plaintiffs' expert testified that the frequency of using tapentadol to treat the noninfringing uses identified by Defendants (purely nociceptive pain or mononeuropathic pain that is severe and chronic) would be minimal. Appx9471-9472 (61:22-62:12); Appx9486 (76:14-23). As to the specific noninfringing uses that either defendant identified, Plaintiffs' expert testified that: (1) "[l]ess than five percent" of patients "are suffering from chronic osteoarthritis due to purely nociceptive pain and require around-the-clock opioid treatment"; (2) "[l]ess than one percent" of patients "are suffering from chronic osteoarthritis due to mononeuropathic pain and require around-the-clock opioid treatment"; and (3) "less than one percent" of patients have chronic diabetic mononeuropathic pain or chronic mononeuropathic post-herpetic neuralgia. Appx11158-11159 (9:13-10:8); Appx11894 (49:2-7).

Plaintiffs' expert explained that the frequency of such noninfringing uses would be rare because, for instance, nociceptive pain is "most often acute" rather than chronic, and that it is "typically . . . not treated with around the clock [medication]," but rather "more with an as needed medication." Appx9472 (62:5-9); Appx9457 (49:9-14). Likewise, mononeuropathic pain is "very rare" to begin with, and "polyneuropathic pain is far more common than mononeuropathic pain." Appx9457 (47:15-18).

IV. Trial

The district court held a bench trial and received post-trial briefing from the parties. *See, e.g.*, Appx7276-7319. Of relevance to this appeal, the court held that: (1) claims 1, 2, 3, and 6 of the '130 patent are not invalid; and (2) Actavis and West-Ward would not infringe the only claims of the '130 patent asserted against them—claims 1 and 2, which recite a method of using tapentadol to treat polyneuropathic pain generally. Appx199.

A. The '130 Patent

The district court held that claims 1, 2, 3, and 6 of the '130 patent are not invalid. Appx175-194. The court also held that Actavis and West-Ward will not induce infringement of or contributorily infringe claims 1 and 2. Appx153-175.

1. Validity

No Anticipation. The court first held that the '737 patent "does not explicitly mention polyneuropathic pain," and therefore does not expressly anticipate the '130 patent claims. Appx176.

The court next held that the '737 patent does not inherently anticipate the '130 patent claims, rejecting Defendants' argument that the '737 patent's disclosure of severe pain "necessarily include[d] a subpopulation with polyneuropathic pain." Appx176-179. The court found that the "context of the '737 patent makes clear that the word 'pain' refer[s] only to nociceptive pain" for two primary reasons: (1) "the only test data for pain treatment disclosed in the '737 patent is from the mouse writhing test, which is a purely nociceptive pain model"; and (2) "the state of the art prior to the filing of the '130 patent was such that when a physician 'discussed opioids in regard to the treatment of severe pain at that time, [s/he] did think nociceptive pain'" only. Appx177. The court further "note[d] that the '737 patent does not appear to enable the practice of the asserted claims of the '130 patent—namely, administration of tapentadol hydrochloride for the treatment of polyneuropathic pain," as there is "no discussion of polyneuropathic pain in the '737 patent and there is no evidence provided regarding the efficacy of tapentadol hydrochloride for treatment of polyneuropathic pain or other considerations (*e.g.*, side effects) regarding its use." Appx179.

No Obviousness-Type Double Patenting. The court rejected Defendants' contention that the '130 patent claims are invalid for obviousness-type double patenting in view of claim 117 of the '593 patent. Appx179-190. First, the court rejected Defendants' argument—which mirrored their anticipation argument—that claim 117's reference to "pain" must necessarily include "polyneuropathic pain." Appx183-185. The court acknowledged that the double patenting analysis was not "limited to what was disclosed within the four corners of the prior art '737 patent" (as it was in the anticipation analysis), but held that claim 117 was "limited to nociceptive pain" because "the nociceptive mouse writhing test . . . provides the only evidence of analgesia in the '593 patent disclosure." Appx183-184. Thus, the court held, claim 117 "does not encompass all of the subject matter of the asserted claims of the '130 patent." Appx184-185.

Second, the court rejected Defendants' argument that, because it was allegedly known that opioids can lower a patient's pain score, "a POSA reading [claim 117] in March 2007 (the filing date of the '130 patent) would have found it obvious to use the compound tapentadol hydrochloride to treat polyneuropathic pain." Appx185-186. The court relied on evidence that: (1) neuropathic pain generally was known to be "refractory to opioids (*i.e.*, either the opioid would be ineffective or would require very high doses to be effective)," and thus "were known to show only limited effectiveness in treating neuropathic pain conditions"; (2)

"[p]rescribing opioids at higher doses," or even lower doses, "can cause serious problems in patients, including side effects "like nausea, vomiting, and constipation" as well as "destruction, dysfunction, or sensitivity of the normal nociceptive pain pathways, which can lead to conditions like hyperalgesia"; and (3) correspondingly, "before, and even after, the 2007 filing date of the '130 patent . . . there was controversy surrounding the usefulness of opioids in treating neuropathic pain." Appx186-188.

Thus, because all of the experts agreed that the "effective *treatment* of polyneuropathic pain involves many considerations other than . . . lower[ing] a patient's pain score," and in view of the widespread controversy, severe side effects, and other problems associated with opioids, the court held that a person of ordinary skill in the art ("POSITA") "would not have had an expectation of successfully *treating* polyneuropathic pain using" simply any drug with opioid mechanisms of action (like tapentadol). Appx187-189. The court held that Defendants failed to "overcome[e] [the] presumption [of validity of the '130 patent] by presenting clear and convincing evidence of obviousness." Appx190.

Objective Indicia of Non-Obviousness. The district court further held that "evidence of unexpected results weigh[ed] in favor of a finding that the" claims "are nonobvious," and that tapentadol "has satisfied a long-felt need in the market for an opioid with lower side effects." Appx193-194. Further, the court held that

"tapentadol hydrochloride had unexpected properties that distinguished it from being 'just another opioid,'" in view of undisputed evidence that Dr. Christoph discovered that:

(1) "tapentadol hydrochloride unexpectedly provided the benefit of treating mononeuropathic pain and polyneuropathic pain at a dose that did not inhibit normal nociceptive pain transmissions," and that "[s]elective inhibition of neuropathic pain without affecting the nociceptive pathway beneficially allows for neuropathic pain treatment without impairing the normal protective mechanisms of nociceptive pain";

(2) "tapentadol hydrochloride is more potent in the treatment of polyneuropathic pain than it is for mononeuropathic pain," which "was surprising . . . because polyneuropathic pain is the more severe condition";

(3) "in the STZ polyneuropathic pain model, tapentadol hydrochloride outperformed morphine," as "less tapentadol was required to achieve the same level of efficacy as morphine, especially because morphine is more potent than tapentadol in other pain models"; and

(4) "tapentadol hydrochloride possesses multiple layers of synergism, which allows lower dosages to be used to achieve desired effects and provides some explanation for [its] other unexpected properties," in addition to a "site-site synergy in the spinal and supraspinal levels (*i.e.*, administering tapentadol hydrochloride into

these two locations results in a synergistic effect) . . . which is relatively rare." Appx191-192.

Finally, the court explained that the evidence demonstrated that "there was a long-felt, unresolved need for a new opioid that could treat chronic pain with lower side effects," such as "constipation, nausea, vomiting, sleepiness, and dizziness," which often resulted in "patients terminating their opioid treatment altogether." Appx193. The court held that tapentadol "has been successful at lowering the side effects experienced by patients taking other extended release opioids" and thus satisfied this long-felt need. Appx193-194. Indeed, tapentadol "was the first" and still is the only "opioid ever approved by the FDA for polyneuropathic pain." Appx11175 (26:18-21); Appx10697 (121:9-12).

2. Infringement

The district court found that Actavis and West-Ward would not infringe claims 1 and 2 of the '130 patent. Even though all of the experts agreed that polyneuropathic pain is a common form of severe chronic pain, that the severe chronic pain indication in Actavis's and West-Ward's labels thus includes polyneuropathic pain, and that an indication instructs as to the products' "intended use or uses," the district court nevertheless found that neither defendant had specific intent to induce infringement. Appx154-171. In addition, the court held that Plaintiffs had met all of the requirements to establish contributory infringement,

except one. The court held that the alleged noninfringing uses of Actavis's and West-Ward's products were substantial solely because they are "not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental," despite unrefuted evidence that the frequency of such uses would be rare. Appx85, Appx173-175.

V. Statement of Joinder

Depomed joins, expressly adopts, and incorporates by reference Grünenthal's response brief in its entirety. *See* Fed. R. App. P. 28(i).

SUMMARY OF ARGUMENT

I. West-Ward's and Alkem's Appeal

The district court correctly held that Defendants failed to prove by clear and convincing evidence that the asserted claims of the '130 patent are not invalid.

First, the court correctly held that the '737 patent does not expressly or inherently anticipate the asserted claims. The '737 patent does not explicitly disclose the treatment of polyneuropathic pain with tapentadol. Likewise, the '737 patent does not necessarily disclose—and is not enabled for—such treatment because the only analgesic data disclosed in the patent is from a test for purely nociceptive pain. Nociceptive pain is wholly separate and distinct from neuropathic (and polyneuropathic) pain, and the treatment of one type is not predictive of the

other. And there was no evidence at the time that any opioid was capable of effectively treating polyneuropathic pain.

Second, the court correctly held that the asserted claims are not invalid for obviousness-type double patenting in view of claim 117 of the '593 patent. The '593 patent is a reissue of the '737 patent, and like the '737 patent, the '593 patent is limited to nociceptive pain treatment and therefore does not disclose polyneuropathic pain treatment. Defendants offered no evidence demonstrating otherwise.

Nor would polyneuropathic pain treatment have been obvious to try. All of the experts agreed that the treatment of such pain involves many considerations other than simply lowering a patient's pain score, such as a patient's quality of life and side effects. As of 2007, there was widespread controversy over the use of opioids, serious side effects associated with them, and limited and contradictory evidence of their effectiveness in treating polyneuropathic pain. Defendants, on the other hand, failed to meet their burden of clear and convincing evidence when they offered only prior art references that were, at best, equivocal on whether opioids were effective for polyneuropathic pain treatment. Indeed, based on the evidence presented, a POSITA would actually have been motivated *against* trying a new opioid like tapentadol to treat polyneuropathic pain.

Finally, the court correctly held that objective indicia of non-obviousness further supported its finding of no invalidity. The court relied on undisputed evidence that it was unexpected and surprising that tapentadol is effective in treating polyneuropathic pain, and that tapentadol has both a synergistic and dose-reduction effect that would not have been predicted. The court likewise correctly found that the evidence demonstrated that tapentadol fulfilled a long-felt need for a new opioid with lower side effects.

II. Plaintiffs' Cross-Appeal

The district court committed clear error in concluding that Actavis and West-Ward would not induce infringement of or contributorily infringe claims 1 and 2 of the '130 patent.

Induced Infringement. All of the experts agreed that polyneuropathic pain is a common form of severe chronic pain, that the severe chronic pain indication in Actavis's and West-Ward's labels includes polyneuropathic pain, and that an indication instructs as to the products' "intended use or uses." In addition, it would be readily apparent to a physician or pharmacist—the target audience for these labels—that the severe chronic pain indication includes polyneuropathic pain even without the words "polyneuropathic pain" being mentioned in the indication. Thus, Actavis and West-Ward will induce infringement of the asserted claims because their labels "will cause at least some users"—in fact, a large number of users—to

directly infringe by using tapentadol to treat polyneuropathic pain. This conclusion is only further confirmed by Actavis's and West-Ward's decision to seek FDA approval of their products despite knowing of these infringement problems.

The district court made several legal and factual errors in holding otherwise, such as improperly relying on noninfringing uses which are legally irrelevant to the inducement inquiry, and incorrectly focusing on whether Actavis and West-Ward intend their products to be used for DPN, where DPN is just one type of polyneuropathic pain.

Contributory Infringement. Plaintiffs presented unrefuted evidence that the alleged noninfringing uses of Actavis's and West-Ward's products would be rare in frequency, and thus could not be substantial. Actavis and West-Ward failed to meet their burden to establish otherwise, and offered only conclusory testimony that the noninfringing uses would not be "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental"—not once addressing the frequency of such uses. Thus, the district court committed clear error by holding that the noninfringing uses would be "substantial" even though the frequency of such uses would be *rare*.

STANDARD OF REVIEW

"Anticipation is a question of fact" that this Court "review[s] for clear error following a bench trial." *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007) (citing *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d

1293, 1304 (Fed. Cir. 2006)). "Under the clear error standard, the court's findings will not be overturned in the absence of a definite and firm conviction that a mistake has been made." *Id.* (quoting *Impax Labs., Inc. v. Aventis Pharm. Inc.*, 468 F.3d 1366, 1375 (Fed. Cir. 2006)) (internal quotation marks omitted). In addition, this Court reviews a district court's "ultimate conclusion" on obviousness-type double patenting *de novo*, and reviews underlying facts for clear error. *See id.* at 1269; *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1376 (Fed. Cir. 2012). This Court also reviews a district court's "factual findings on the [objective indicia of non-obviousness] for clear error." *Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1376 (Fed. Cir. 2000) (citation omitted).

Finally, after a bench trial, "infringement is a question of fact reviewed for clear error." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010) (quoting *Golden Blount, Inc. v. Robert H. Peterson, Co.*, 438 F.3d 1354, 1361 (Fed. Cir. 2006)) (internal quotation marks omitted); *see also Eli Lilly & Co. v. Teva Parenteral Medicines*, 845 F.3d 1357, 1364 (Fed. Cir. 2017).

ARGUMENT ON WEST-WARD'S AND ALKEM'S APPEAL

"Since [this Court] must presume a patent [to be] valid, the patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). The Supreme Court has made clear that the clear and convincing evidence

standard imposes upon a patent challenger "a heavy burden of persuasion" and "heightened standard of proof." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 101-02 (2011) (citation and internal quotation marks omitted). The Supreme Court explained that "Congress is presumed to have chosen" that "high bar" for a patent challenger to meet given that every issued patent "is 'presumed valid.'" *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1929 (2015).

Here, the district court correctly held that Defendants failed to meet their burden of proving by clear and convincing evidence that the asserted claims of the '130 patents are invalid. The court's judgment as to those issues, set forth in a detailed, highly factual, 167-page opinion, should be affirmed.

I. The District Court Correctly Held That the Asserted Claims of the '130 Patent Are Not Invalid

The district court correctly held that Defendants failed to prove by clear and convincing evidence that the asserted claims of the '130 patent are invalid for anticipation or obviousness-type double patenting.

A. The '737 Patent Does Not Anticipate the '130 Patent Claims

The district court correctly held that the '737 patent discloses only the treatment of nociceptive pain, and thus does not expressly or inherently anticipate the '130 patent claims, which only recite a method of treating polyneuropathic pain. Appx175-179; Appx11160 (11:6-10).

To establish anticipation, "a single prior art reference" must disclose "each and every" claim limitation of the challenged claims. *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). The analysis is limited to what is disclosed in the "four corners of [the] single prior art document." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (citations and internal quotation marks omitted). Disclosure may be explicit or inherent, *Schering*, 339 F.3d at 1377, but "anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation." *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007) (emphasis in original).

Furthermore, "[a]n anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). In other words, the reference "must [have] sufficiently describe[d] the claimed invention to have placed the public in possession of it." *Elan Pharm., Inc. v. Mayo Foundation for Med. Educ. & Res.*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (citation and internal quotation marks omitted).

No Express Anticipation. It is "undisputed that the '737 patent does not explicitly mention polyneuropathic pain" or the treatment thereof with tapentadol.

Appx176; Appx11160 (11:11-19); Appx10655 (79:21-23). Defendants failed to present any contrary evidence. Thus, the district court correctly held that the '737 patent does not expressly anticipate the '130 patent claims. Appx176.

No Inherent Anticipation. The district court also correctly held that the '737 patent does not "necessarily" disclose the treatment of polyneuropathic pain with tapentadol, and thus does not inherently anticipate the '130 patent claims. Appx176-179. Defendants' own expert conceded that the '737 patent does not "necessarily disclose polyneuropathic pain or the treatment [of] polyneuropathic pain." Appx10465 (118:17-20); Appx10752-10753 (176:23-177:3); *see also* Appx11160-11161 (11:24-12:2).

The court correctly found that although the '737 patent discloses "pain" and "severe pain," its disclosure is limited to nociceptive pain. Appx176-179. All of the experts agreed that nociceptive pain is separate and distinct from neuropathic (including polyneuropathic) pain, and the treatment of one type is not predictive of the other—in fact, polyneuropathic pain is particularly difficult to treat, while nociceptive pain is not. Appx9387 (39:9-10); Appx11266-11267 (117:21-118:23); Appx11161-11162 (12:25-13:21); Appx11180 (31:9-13); Appx11187-11188 (38:21-39:15); Appx11219 (70:20-22); Appx10380-10382 (33:6-35:9); Appx10704 (128:6-8); Appx9188-9189 (167:21-168:5); Appx9189-9190 (168:17-169:8); Appx9191 (170:1-7).

The court explained that "the only test data for pain treatment disclosed in the '737 patent is from the mouse writhing test, which" all of the expert witnesses agreed "is a purely nociceptive pain model." Appx177; Appx9287 (266:17-19); Appx9319 (298:19-23); Appx9340-9341 (319:18-320:13); Appx10692-10693 (116:23-117:20). The '130 patent, on the other hand, discloses analgesic data specifically from polyneuropathic pain models, such as the STZ models. *See, e.g.*, Appx436-438 ('130 patent, 14:7-17:22). For these same reasons, the court also correctly observed that the '737 patent is not enabled for the treatment of polyneuropathic pain because it lacks *any* data or disclosure supporting that—or how—tapentadol could be effective for that purpose. Appx179; *see also Sanofi-Synthelabo*, 550 F.3d at 1082 (holding that a reference could not anticipate because it was not enabled).

In addition, the court correctly found that a POSITA would have understood the terms "pain" or "severe pain" in the context of the '737 patent to refer only to nociceptive pain. The court relied on expert testimony and evidence dictating that "the state of the art . . . was such that when a physician 'discussed opioids in regard to the treatment of severe pain . . . [s/he] did think nociceptive pain'" and not polyneuropathic pain. Appx177-178. This was because, at the time, it was widely understood by physicians that opioids (like tapentadol) could not treat neuropathic pain due to their limited mechanism of action. Appx188; Appx58359-58387;

Appx58437-58451; Appx58529-58536; Appx58537-58546; Appx58547-58598; Appx58518-58528; Appx11163 (14:5-8). Thus, the court held that absent "any context [in the '737 patent] to specifically indicate neuropathic pain," a POSITA reading the term "pain" in the patent would "default to nociceptive pain." Appx178.

Although West-Ward disputes the district court's factual determinations, it fails to identify any clear and convincing evidence that the '737 patent "necessarily" discloses polyneuropathic pain treatment. First, West-Ward argues that the mouse writhing test did not "'clearly set forth a ***definition*** of" "pain" or "severe pain." West-WardBr. 48 (emphasis added). That contention is flatly wrong, in view of the undisputed evidence demonstrating that the mouse writhing test is well-known and well-established to be limited to purely nociceptive pain. Even if it were not, West-Ward fails to identify any contrary evidence.

Second, West-Ward argues that "the population [of patients] with 'severe pain' described in the '737 patent necessarily includes a subpopulation with polyneuropathic pain." West-WardBr. 45. This argument, however, is based on an entirely incorrect assumption that the '737 patent addresses the treatment of all types of pain. It does not. As discussed above, the '737 patent addresses *only* the treatment of "severe pain" patients with *purely nociceptive pain*; the patent does not address *all* severe pain patients, let alone *all* pain patients generally. Thus, the population of patients with severe, purely nociceptive pain, as addressed in the '737 patent, does

not include a subpopulation of *any* polyneuropathic pain patients. Appx11162 (13:4-21). Indeed, as discussed below, the '737 patent is only enabled for the treatment of purely nociceptive pain, and thus says nothing to whether tapentadol could effectively treat polyneuropathic pain, which is separate and distinct from nociceptive pain.

Third, West-Ward suggests that the '737 patent "necessarily" discloses polyneuropathic pain treatment because the "genus of 'pain' and 'severe pain'" is "limited [in] number." West-WardBr. 43. As an initial matter, West-Ward identifies no evidence relating to the scope of the genus of "pain" or "severe" pain, which is an argument that Defendants failed to raise before the district court and thus waived. *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1296 (Fed. Cir. 2009) ("If a party fails to raise an argument before the trial court, or presents only a skeletal or undeveloped argument to the trial court, we may deem that argument waived on appeal."). Regardless, genus size is not dispositive of the issue, as explained even in the decisions on which West-Ward relies (which, in any event, involve only composition claims and not method of treatment claims). West-WardBr. 43. For instance, in *In re Petering*, 301 F.2d 676 (C.C.P.A. 1962), this Court's predecessor court stated that it is not the "*mere number*" of species in a genus that dictates the anticipation analysis, "but, rather, the *total circumstances involved*," including the disparities and variations in the species of the genus. *Id.* (emphasis added). Here, it

is undisputed that nociceptive pain is wholly separate and distinct from polyneuropathic pain, and the treatment of one is not predictive of the other.

Fourth, West-Ward argues that the district court "had no proper basis to limit" the term "pain" in the '737 patent to "nociceptive pain." West-WardBr. 47-48. West-Ward itself, however, fails identify *any* "proper basis" in the '737 patent to conclude that its reference to "pain" must necessarily *include* polyneuropathic pain. *Id.* Because Defendants failed to present any such evidence, the district court was correct to assess what the '737 patent and its claims disclosed to the public by referring to the specification, which is "dispositive" of and "the single best guide to the meaning" and scope "of a disputed term." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (citation omitted); Appx177-179. And based on that assessment, the district court correctly found that the only analgesic data disclosed in the '737 patent was for purely nociceptive pain, and thus that its scope is limited to such pain. *See MagSil Corp. v. Hitachi Global Storage Techs.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012) ("[T]he scope of [patent] claims must be less than or equal to the scope of the [patent's] enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims.").

Finally, West-Ward asserts that the "'737 patent is presumed enabled" for polyneuropathic pain treatment, but provides no evidence in support. West-WardBr.

48. Once again, West-Ward incorrectly assumes that patients suffering from polyneuropathic pain must be subsumed within a population of nociceptive pain sufferers to whom the patent is directed. West-Ward then compounds its shortcomings by failing to acknowledge that, to the extent there is a presumption of enablement, that presumption "may [be] overcome" if "undue experimentation would be required to achieve enablement." *See Sanofi-Synthelabo*, 550 F.3d at 1085; *Impax Labs., Inc. v. Aventis Pharm., Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008). Here, as the district court correctly found, there would be "undue experimentation . . . required to achieve enablement" because "there is no evidence provided [in the '737 patent] regarding the efficacy of tapentadol hydrochloride for the treatment of polyneuropathic pain or other considerations (*e.g.*, side effects)." Appx179.

Thus, the district court correctly held that Defendants failed to prove by clear and convincing evidence that the '737 patent anticipates the '130 patent claims.

B. The '130 Patent Claims Are Not Invalid for Obviousness-Type Double Patenting

The district court correctly held that "the asserted claims of the '130 patent are patentably distinct from claim 117 of the '593 patent," and therefore that the '130 patent claims are not invalid for obviousness-type double patenting. Appx179-194. Like the '737 patent, the '593 patent is limited to the treatment of nociceptive pain, which is separate, distinct, and not predictive of polyneuropathic pain treatment.

"The doctrine of obviousness-type double patenting . . . prohibit[s] the issuance of the claims in a second patent not patentably distinct from the claims of [a] first patent." *Eli*, 689 F.3d at 1376 (citation omitted). "A later patent claim is not patentably distinct from an earlier claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.* (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001)) (internal quotation marks omitted).

Furthermore, "[a]s a general rule, obviousness-type double patenting determinations turn on a comparison between a patentee's earlier and later claims, with the earlier patent's written description considered only to the extent necessary to construe its claims." *Id.* at 1378-79. "The focus of the obviousness-type double patenting doctrine thus rests on preventing a patentee from claiming an obvious variant of what it has previously *claimed*, not what it has previously *disclosed*." *Id.* at 1379 (emphasis in original).

1. "Pain" in the '593 Patent Does Not Necessarily Include Polyneuropathic Pain

The district court correctly held that the treatment of "pain" in claim 117 of the '593 patent does not necessarily include polyneuropathic pain treatment, because—like with the '737 patent, of which the '593 patent is a reissue—the '593 patent only claimed the treatment of nociceptive pain.

Here, the district court correctly held that "the disclosure of the '593 patent is essentially identical to the disclosure of the '737 patent," and thus the "conclusion"

that the '737 patent does not anticipate the '130 patent claims "remains the same with respect to [the] obviousness-type double patenting" inquiry regarding the '593 patent. Appx183-185. Because the double patenting analysis focuses on a comparison of what was "previously claimed," the court properly focused on the "question of what 'pain' means in claim 117 of the '593 patent." Appx184. And the court correctly held that Defendants failed to prove by clear and convincing evidence that "pain" recited in claim 117 necessarily includes polyneuropathic pain, holding that "Defendants' outside evidence does not outweigh the evidence presented as to the context of the '593 patent—namely, the nociceptive mouse writhing test that provides the only evidence of analgesia in the '593 patent disclosure." *Id.*

West-Ward now attempts to rely on extrinsic references to argue that a POSITA would have simply read "pain" in claim 117 to include all types of pain because it was allegedly "well-known" that opioids were "effective for treating all types of pain, including polyneuropathic pain." West-WardBr. 54-55; Appx86-87. As a preliminary matter, and as discussed further below, it was *not* "well-known" that opioids were "effective" in treating polyneuropathic pain—in fact, the opposite was true, as opioids were considered to be ineffective and their use was highly controversial for many reasons.

Regardless, none of these references answer the question of what was "previously *claimed*" in claim 117 of the '593 patent—the focus of the double patenting inquiry. *Eli Lilly*, 689 F.3d at 1378-79 (emphasis in original). West-Ward fails to identify any clear and convincing evidence supporting how the '593 patent "previously claimed" polyneuropathic pain treatment without any "evidence of [such treatment] in the '593 patent disclosure." Appx184. Indeed, if claim 117 included polyneuropathic pain treatment within its scope, then it would surely be invalidated for lack of written description and enablement given that there is nothing in the '593 patent specification supporting such claim scope. The district court was therefore correct to rely on the '593 patent's specification to determine the scope of claim 117, and was likewise correct to conclude that, based on the fact that the only analgesic data disclosed in the '593 patent was for purely nociceptive pain, the '593 patent (and its claim 117) only claimed the treatment of purely nociceptive pain with tapentadol. Appx183-184; *Phillips*, 415 F.3d at 1315. Thus, the court correctly held that Defendants failed to demonstrate that the '593 patent necessarily disclosed polyneuropathic pain treatment.

2. A POSITA Would Have Been Motivated *Against* Trying a New Opioid Like Tapentadol to Treat Polyneuropathic Pain

The district court correctly held that Defendants failed to meet "their burden of demonstrating by clear and convincing evidence that a POSA would have had a

reasonable expectation that tapentadol hydrochloride would be effective to treat polyneuropathic pain." Appx188.

As an initial matter, although West-Ward argues on appeal that "the treatment of polyneuropathic pain with tapentadol hydrochloride was merely an obvious variant of treating nociceptive pain," Defendants never raised, and thus waived, the specific argument below. *Compare* West-WardBr. 57, *with* Appx7353-7356 (never raising an "obvious variant" argument or even using the phrase); *Fresenius*, 582 F.3d at 1296. In any event, it is undisputed that nociceptive pain and neuropathic pain are separate and distinct, and the treatment of one is not predictive of the other. Treating polyneuropathic pain therefore cannot be an "obvious variant of treating nociceptive pain," and West-Ward fails to present any clear and convincing evidence otherwise. West-WardBr. 57.

The argument that Defendants *actually* attempted (and failed) to prove at trial was that "[a]t a minimum, a POSITA would be motivated to at least *try* treating polyneuropathic pain with tapentadol." Appx7375-7378 (arguing that a POSITA would "at least try tapentadol in an animal model of polyneuropathic pain and to expect success"); West-WardBr. 58; Appx7355-7356.

The district court correctly held that Defendants failed to meet their burden. Appx185-189. The court considered significant evidence and expert testimony that "the standard was not to prescribe opioids for neuropathic pain because": (1)

"neuropathic pain was generally considered to be unresponsive to opioids"; (2) opioids "can cause serious problems in patients, including side effects (like nausea, vomiting, and constipation)"; (3) "[h]igh doses of opioids can [] cause destruction, dysfunction, or sensitivity of the normal nociceptive pathways"; and (4) there was—and still is—a serious "controversy surrounding the usefulness of opioids in treating neuroapthic pain" in 2007. Appx186-187. And the court relied on the testimony of the parties' experts, who all agreed that "the effective treatment of polyneuropathic pain involves *many considerations other than* simply identifying a drug that exhibits efficacy in *lowering a patient's pain score*." Appx187 (emphasis added).

Based on these facts, the district court correctly held that Defendants not only failed to "demonstrat[e] by clear and convincing evidence that a POSA would have had a reasonable expectation that tapentadol hydrochlorie would be effective to treat polyneuropathic pain," but that they also failed to "*rebut*[] *Plaintiffs' evidence* that the treatment of pain involves more than efficacy alone and a POSA *would not* have had an expectation of successfully treating polyneuropathic pain using tapentadol hydrochloride." Appx188-189 (emphasis in original).

On appeal, West-Ward argues that the district court applied too great a hurdle to overcome. West-Ward's dispute with the court's holding is two-fold: (1) the "treatment of pain" only requires lowering a patient's pain score; and (2) although portions of certain references admittedly discussed the widespread controversy over,

and the ineffectiveness of, using opioids in treating polyneuropathic pain, other portions of those references suggest that opioids can lower pain score. West-WardBr. 59-62. West-Ward's arguments fail to demonstrate that the district court committed clear error, as they contradict Defendants' own expert's testimony and offer evidence that is, at best, equivocal on the issue.

1. The treatment of pain involves several considerations other than simply lowering pain score. This Court has "made clear . . . that the 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." *Phillips*, 415 F.3d at 1313 (citations omitted); *see also Howmedica Osteonics Corp. v. Zimmer, Inc.*, 822 F.3d 1312, 1320-21 (Fed. Cir. 2016) ("[A] skilled artisan reads a claim term not only in the context of the claim at issue, but also in the context of the entire patent, including the written description and prosecution history, as well as the extrinsic evidence.").

Here, even Defendants' expert agreed that a POSITA considered treatment to involve many considerations other than simply lowering pain score, such as a patient's quality of life and whether serious side effects will result in a patient terminating use of a medication. Appx10671 (95:15-18); *see also* Appx11173 (24:2-11). Thus, the district court correctly relied on this undisputed expert testimony to hold that effective treatment is not simply about lowering pain score. Appx187.

Nevertheless, West-Ward argues that "[t]he claimed method only has to 'treat[]' (i.e., *reduce*) polyneuropathic pain." West-WardBr. 60. But West-Ward identifies no evidence presented at trial to support its argument. *Id.* Nor could it, as Defendants' own expert agreed that effective treatment is not simply about lowering pain score. Instead, West-Ward attempts to rely on a portion of the '130 patent specification even though the focus of the doule patenting analysis is on the *claims*. *Eli Lilly*, 689 F.3d at 1378-79. Ironically, the portion of the specification on which West-Ward relies only further disproves its argument: the specification explains that "treat[ment]" of neuropathic pain is "effective[]" only where there are no "excessive side effects," which again confirms that the effective treatment of pain involves considerations *other than* simply lowering pain score. Appx430 ('130 patent, 2:40-42). Thus, West-Ward's attempt to ignore the undisputed evidence as to the meaning of "treatment" should be rejected.

2. The widespread controversy, serious side effects, and limited evidence of efficacy associated with opioids. The evidence at trial confirmed that there was widespread controversy over the use of opioids in treating neuropathic pain, that opioids caused serious side effects that often resulted in a patient terminating use of the medication, and that there was limited evidence of their use in treating polyneuropathic pain. *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1343 (Fed.

Cir. 2011) ("Whether the prior art teaches away from the claimed invention is a question of fact.").

"[T]he standard was not to prescribe opioids for neuropathic pain." Appx11163 (14:5-8). For instance, opioids were known to cause severe side effects, including "constipation, nausea, vomiting, sleepiness, [and] dizziness." Appx11175-11176 (26:22-27:5). Because of these side effects, patients often could not "tolerate" the medication and terminated use of the medication altogether. *Id.* Furthermore, POSITAs viewed neuropathic pain and polyneuropathic pain as "refractory to opioids," meaning that opioids were ineffective or "require[d] much higher doses." Appx11163 (14:6-8); Appx11164 (15:4-8). And prescribing opioids at higher doses caused "significant issues," including hormone changes, side effects, and a "dysfunction or sensitivity" of the normal nociceptive pain pathways, including hyperalgesia. Appx11164 (15:15-25); Appx11165 (16:3-10). Thus, even if a POSITA might have considered using opioids to treat polyneuropathic pain in rare instances, it was only "out of desperation." Appx11163 (14:18-25). But prescribing a drug "out of desperation" is "not [] a form of treatment." *Id.*

Based on this evidence, the district court correctly held that Defendants failed to establish the contrary by clear and convincing evidence. In fact, the court found that Defendants' *own* prior art references confirmed the existence of the widespread controversy over the use of opioids and the limited evidence of their efficacy in

treating polyneuropathic pain. Appx185-188. West-Ward concedes that Defendants' Namaka reference, for instance, disclosed that "the treatment of chronic neuropathic pain is often debated and not very well studied," "effectiveness is variable and responsiveness may vary across the different types of neruropathic pain syndromes," and that "there is limited assessment of opioid effectiveness in neuropathic pain." Appx58359-58388 at Appx58372. Defendants' Baron reference likewise acknowledged that the "widespread opinion" that neuropathic pain is not "opioid sensitive." Appx58407-58422 at Appx58414. Furthermore, Defendants' Dworkin 2007 reference explained that:

> [T]he management of patients with chronic [neuropathic pain] is complex and response to existing treatments is often inadequate. Even with well-established [neuropathic pain] medications, ***effectiveness is unpredictable,*** dosing can be ***complicated***, analgesic onset is ***delayed***, and ***side effects are common***.

Appx58437-58451 at Appx58438 (emphasis added).

Even Defendants' expert published an article stating that "[t]he use of opioids for the treatment of neuropathic pain remains controversial. Appx58537-58546 at Appx58541. Likewise, Defendants' expert "provide[d] input" on guidelines from the Center for Disease Control and Prevention which concluded, "No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain," and "[e]xtensive evidence shows the possible harms of opioids." Appx58547-58598 at Appx58563; Appx10672-10673 (96:24-97:2). Thus,

Defendants' own prior art references and expert testimony contradict West-Ward's very argument on appeal that there was no "conflicting evidence" over the use of opioids in treating polyneuropathic pain. West-WardBr. 61.

West-Ward nevertheless attacks the district court's factual assessment of these references by arguing that, for instance, the Namaka and Dworkin references disclose that opioids can lower pain score. West-WardBr. 61-62. Similarly, West-Ward argues that the Gilron reference on which the court relied demonstrates that opioids were "found to be effective for *reducing* neuropathic pain." West-WardBr. 62 (emphasis added). But again, such disclosures at best *only* relate to whether opioids can *lower a patient's pain score* which, as explained above, is just one of many other considerations in effectively treating polyneuropathic pain. *See, e.g.*, Appx58518-58528 at Appx58527 (referring only to "patients' total scores for the intensity of pain"); Appx58359-58387 at Appx58372 (referring only to "associated pain scores" and "pain reduction" related to the use of opioids for "post-nerve injury" and "peripheral neuropathic pain" as identified by Defendants).

Thus, West-Ward's argument on appeal is that Defendants presented the district court with prior art references that, at worst (for Defendants), *teach away* from trying a new opioid to treat polyneuropathic pain or, at best (for Defendants), are merely *equivocal* about the use of opioids in effectively treating polyneuropathic pain. West-WardBr. 61-63. Strikingly absent from West-Ward's brief is *clear and*

convincing evidence that a POSITA would have found it obvious to try tapentadol in treating a patient suffering from polyneuropathic pain despite the widespread controversy over opioid use and the limited evidence of their efficacy in treating polyneuropathic pain. West-Ward, instead, asks this Court to ignore this opioid controversy altogether, and to accept its startling *ipse dixit* that whether a drug is "controversial" would be "entirely *irrelevant*" to a POSITA (*i.e.*, a pain doctor) in deciding whether to prescribe an opioid to treat a patient with polyneuropathic pain. West-WardBr. 63 (emphasis added).

Thus, the district court correctly held that Defendants failed to prove by clear and convincing evidence that the '130 patent claims are invalid for obviousness-type double patenting.

3. Objective Indicia of Non-Obviousness Further Confirm That the Asserted Claims of the '130 Patent Were Not Obvious

Finally, the district court correctly held that objective indicia of non-obviousness—namely, unexpected results and long-felt need—further confirm that the '130 patent claims were not obvious. Appx191-194. At trial, Defendants failed to attack or proffer any countervailing evidence that would challenge the significant evidence of unexpected results and long-felt need. Now on appeal, West-Ward provides no legal basis for ignoring the unrefuted evidence of non-obviousness discussed below.

"The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis. Indeed, [this Court has] held that 'evidence of secondary considerations may often be the most probative and cogent evidence in the record.'" *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (citations omitted); *see also Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) (quoting *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010)) ("Objective indicia of non-obviousness 'can be the most probative evidence of non-obviousness in the record, and enables the court to avert the trap of hindsight.'"). "Objective indicia minimize hindsight's impact," *WBIP*, 829 F.3d at 1337, and often outweigh evidence of obviousness, particularly where the evidence regarding objective indicia are undisputed. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) (affirming the district court's rejection of the defendant's obviousness and obviousness-type double patenting arguments).

In addition, "there is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP*, 829 F.3d at 1329. Although that presumption is rebuttable, the "patent

challenger" must "present[] evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *Id.*

West-Ward incorrectly argues that objective indicia of non-obviousness "cannot displace [a] strong *prima facie*" case of obviousness. West-WardBr. 64. As discussed above, Defendants failed to establish a *prima facie* case of obviousness, let alone a "strong" one. And in any event, this Court in *WBIP* rejected Defendants' very assertion that "non-obviousness can never overcome a strong prima facie case of obviousness," explaining that such an assertion is a "misperce[ption of] the obviousness inquiry," as "the strength" of these objective indicia "must be weighed in every case and must be weighted en route to the final determination of obviousness or non-obviousness." *WBIP*, 829 F.3d at 1328-29; *see also Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) ("Whether before the Board or a court, this court has emphasized that consideration of the objective indicia is *part of* the whole obviousness analysis, not just an afterthought.") (emphasis in original).

a) Unexpected Results

"[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "Unexpected results are" therefore "useful to show the 'improved properties provided by the claimed compositions are much greater than would have been

predicted." *Leo*, 726 F.3d at 1358. Thus, the reasonable expectation of success necessary to prove obviousness is unlikely to exist where the claimed compound possesses unexpected therapeutic properties. *See, e.g.*, *In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 517-18 (Fed. Cir. 2012). Finally, when a patentee "demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *Soni*, 54 F.3d at 751 (emphasis in original).

Here, Plaintiffs presented the following undisputed evidence of tapentadol's unexpected results in effectively treating polyneuropathic pain, which even Defendants' own expert praised in a 2011 article published *after* the '130 patent was filed and itself published.

First, tapentadol unexpectedly treats mononeuropathic and polyneuropathic pain without destroying the normal nociceptive pain pathways as opioids typically do. Appx11731-11738 (40:2-47:15); Appx56742-56846 (Tab 1); Appx56619-56633 at Appx56627; Appx56577-56591.

Second, tapentadol possesses a higher potency for treating polyneuropathic pain over mononeuropathic pain, which is surprising given that polyneuropathic pain causes more severe pain. Appx11704 (13:12-23); Appx11738-11739 (47:16-48:13); Appx56742-56846 at Appx56823-56825.

Third, in treating polyneuropathic pain, tapentadol is more potent than morphine—the "gold standard" for treating nociceptive pain—which is "astonishing" since morphine is more potent than tapentadol in other pain models, and because tapentadol is an opioid-like drug. Appx56742-56846 at Appx56827 (Tab 1); Appx11743-11745 (52:1-54:1); Appx9359 (11:16-21); Appx9360 (12:14-20).

Fourth, tapentadol surprisingly possesses "intrinsic" synergy between its multiple mechanisms of action in treating neuropathic pain and "site-site" synergy in the spinal and supraspinal levels. Appx11750-11757 (59:11-66:5); Appx56647-56655; Appx56711-56718.

Finally, the data unexpectedly showed that tapentadol selectively inhibits neuropathic pain over nociceptive pain. Appx434, ('130 patent, Table 1 ("ipsi" refers to neuropathic pain, and "contra" refers to nociceptive pain)); Appx436, ('130 patent, Table 2 ("diabetes" refers to polyneuropathic pain)); Appx56742-56846, 56848 (Tab I); Appx11731 (40:19-25, 40:2-9); *see also* Appx56619-56633; Appx56577-56591.

The experts confirmed the unexpectedness of these results in each of the foregoing categories. Before he was retained as an expert in this litigation, Defendants' expert, Dr. Buvanendran, published an article about the "***novel*** central acting analgesic with du[a]l mode of action" and that its "du[a]l mode of analgesia

is ***synergistic***." Appx58599-58603 at Appx58602 (emphasis added). Plaintiffs' expert agreed, testifying that when NUCYNTA® ER was approved in 2011, those in the art were "surprised and amazed" to see that a large-scale study using a pure neuropathic pain model showed such efficacy in treating polyneuropathic pain—which had never been seen before. Appx11175 (26:7-17). Indeed, tapentadol "was the first" and is still the *only* "opioid ever approved by the FDA for polyneuropathic pain." *Id.* (26:18-21); Appx10468 (121:9-12).

Defendants presented no contrary evidence at trial. Thus, "*in the absence of* evidence to the contrary," Plaintiffs' undisputed evidence of unexpected results discussed above "suffice to establish unexpected results." *Soni*, 54 F.3d at 751 (emphasis in original). Nevertheless, West-Ward raises another new argument on appeal; namely, that the unexpected results inquiry "must [] be tied to the difference between" the methods of the later-expiring and earlier-expiring patents, and that none of the unexpected results relate to a comparison between treating polyneuropathic pain (the '130 patent) and treating nociceptive pain (the '593 patent). *Compare* West-WardBr. 65-66, *with* Appx7350-7352. Yet the authorities on which West-Ward relies contain no such requirement. West-WardBr. 65-66. Regardless, West-Ward's bare assertion directly contradicts the evidence, which demonstrates that—as discussed above—the unexpected results *did* relate to a comparison between treating polyneuropathic pain and nociceptive pain.

Appx11731 (40:19-25) ("[W]e don't find any—at the same dose, we don't find any strong effect [from tapentadol] on the nociceptive system"); *id.* (40:2-9) (discussing what effects that opioids would "characteristically" have on the "nociceptive" pain system); *see also* Appx56619-56633; Appx56577-56591.

West-Ward's remaining arguments should similarly be rejected, including its unsupported statements that the "results cannot be said to be truly 'unexpected' anyway" and that "Dr. Christoph never discussed what was expected or unexpected as of the filing date for the '130 patent"—which wholly ignores the evidence discussed above. West-WardBr. 66. Furthermore West-Ward's argument that Dr. Christoph "never compared his results to tramadol" directly contradicts his testimony at trial and Defendants' own concession in the district court that Plaintiffs did "compare tapentadol to its parent compound, tramadol." *Id.*; Appx7351. In addition, West-Ward fails to even acknowledge the significant differences between tapentadol and tramadol, including that tramadol is a weak opioid that must be administered as a racemic mixture. Appx11756-11757 (65:15-66:7); Appx11777-11778 (86:8-87:1).

b) Long-Felt, Unmet Need

"Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP*, 829 F.3d at 1332.

The district court reached its decision after carefully considering evidence that tapentadol met a long-felt, unresolved need for a new opioid that could treat polyneuropathic pain with lower side effects. Appx11175-11176 (26:22-27:5); Appx11177 (28:8-12); Appx60542-60550 at Appx60542. For instance, whereas side effects occur at least 80% of the time with other opioids, the incidence of such side effects with tapentadol is only 13 to 15%—a "dramatic reduction." Appx11176-11177 (27:18-28:4). Even Defendants' expert, Dr. Buvanendran, acknowledged these lower side effects in 2011: "For equipotent doses of narcotics, tapentadol has ***decreased*** incidence of nausea and vomiting compared to oxycodone," which he considered a "***great benefit***." Appx58599-58603 at Appx58602 (emphasis added); *see also* Appx60530-60541 at Appx60530 (noting tapentadol's reduced side effects and other benefits).

Furthermore, several articles discussed the serious side effects of opioids and how tapentadol met the need for a new opioid with lower side effects:

- "Many patients are not being treated adequately, for reasons that include concerns over tolerability, as well as with addiction issues . . . An important reason for the ***discontinuation of opioid therapy*** is due to concerns over the ***tolerability profile*** of this drug, particularly with *strong opioids* such as morphine. The major reasons for ***discontinuation*** of opioid analgesic treatment are gastrointestinal ***side effects***," such as "nausea, vomiting, and constipation, along with central nervous system side effects." Appx60542-60550 at Appx60542 (emphasis added).

- "A novel approach is to combine more than one analgesic principle in one molecule so that both mechanisms are pharmacologically engaged. ***This concept was realized in tapentadol*****,** a compound purposely designed to

combine two analgesic actions, Mu-opioid receptor agonist activity with norepinephrine reuptake inhibition. In this case, the analgesic effect is ***not reliant solely on agonist activity at Mu receptor that is also responsible for side effects***." Appx60530-60541 at Appx60530 (emphasis added).

- "Specifically, the ***reduction*** in treatment-emergent gastrointestinal ***adverse effects for tapentadol*** compared with equianalgesic pure Mu-opioid receptor agonists results in ***improved tolerability*** and ***adherence to therapy*** for both the immediate- and extended-release formulations of ***tapentadol***. Appx60542-60550 at Appx60542 (emphasis added).

Although West-Ward presents no contrary evidence, it nonetheless argues that "there was no long-felt need for another opioid treatment option" because "opioids were second-line treatments for polyneuropathic pain then and remain so today." West-WardBr. 67. But West-Ward misses the point—the long-felt need was not just for another opioid, but specifically one that could effectively treat such pain *with lower side effects*.

In addition, West-Ward presents another new argument on appeal that there is no "nexus" between the evidence demonstrating that tapentadol met a long-felt need and the claimed invention of the '130 patent. *Compare* West-WardBr. 67 *with* Appx7352-7353. West-Ward, though, fails to rebut the "presumption of nexus" with any "evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *WBIP*, 829 F.3d at 1329. West-Ward wholly misunderstands the nexus requirement, which requires only that the "asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *Id.* at 1329. Here, the evidence that tapentadol

is effective in treating polyneuropathic pain with lower side effects is unquestionably "tied to" the compound (tapentadol), and tapentadol (and the use thereof to treat polyneuropathic pain) indisputably "is the invention disclosed and claimed in the ['130] patent." *Id.* The inquiry ends there. Whether the claims of the '130 patent can or should be construed to require "'extended release' of tapentadol hydrochloride or 'lower side effects,'" as West-Ward now argues, is completely irrelevant to whether there is nexus between the evidence and the invention. West-WardBr. 67.

* * * * *

Accordingly, the district court correctly held that Defendants failed to establish by clear and convincing evidence that the asserted claims of the '130 patent are invalid. The court's judgment of no invalidity should therefore be affirmed.

ARGUMENT ON PLAINTIFFS' CROSS-APPEAL

This Court should reverse the district court's judgment that Actavis and West-Ward will not induce infringement of or contributorily infringe claims 1 and 2 of the '130 patent.

I. The District Court Erred in Concluding That Actavis and West-Ward Would Not Induce Infringement of the '130 Patent

Actavis's and West-Ward's labels will each cause physicians, pharmacists, and patients to use their tapentadol products to treat polyneuropathic pain because the labels contain an indication for severe chronic pain. Because polyneuropathic

pain is one of the most common forms of severe chronic pain—a fact that would be readily apparent to at least a physician or pharmacist reading the indication, Actavis and West-Ward will induce infringement of claims 1 and 2 of the '130 patent, which recite a method of treating polyneuropathic pain with tapentadol.

A. A Drug Label Will Induce Infringement if It "Will Cause at Least Some Users" to Infringe

To prove direct infringement, "a patentee must show," "by either direct or circumstantial evidence," "that an accused product or method meets every claim limitation either literally or under the doctrine of equivalents." *See Pfizer, Inc. v. Teva Pharm., USA, Inc.*, 429 F.3d 1364, 1376 (Fed. Cir. 2005); *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1219 (Fed. Cir. 2006) (citation omitted).

To establish induced infringement, a patentee is required to demonstrate that an infringer "knowingly induced infringement and possessed specific intent to encourage another's [direct] infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010). "[D]irect evidence" of intent "is not required; rather, circumstantial evidence may suffice." *Sanofi v. Watson*, No. 2016-2722 et al., --- F.3d ---, 2017 WL 5180716, at *5 (Fed. Cir. Nov. 9, 2017) (citation and internal quotation marks omitted). Furthermore, unlike a patent challenger's high burden of proving invalidity by clear and convincing evidence, a patentee's burden to prove infringement is by a "preponderance of the evidence," which requires only

that infringement is "more likely than not." *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 449 F. App'x 923, 928 (Fed. Cir. 2011) (citation omitted).

In the Hatch-Waxman context, because the generic drug is not actually on the market at the time of litigation, specific intent is typically inferred from a generic's proposed drug label. *See, e.g.*, *Sanofi*, 2017 WL 5180716, at *7. "[E]xplicit [] commands" and words are not required to find specific intent. *Id.* In addition, a generic's "decision to proceed with its plan to distribute the [generic] drug" and "to continue seeking FDA approval of those instructions" in its drug label, "despite being aware that the label presented infringement problems," "may be sufficient evidence of specific intent to induce infringement." *See id.*; *Eli Lilly*, 845 F.3d at 1368-69; *Apotex*, 633 F.3d at 1059-61.

In *Apotex*, this Court held that if label instructions "*will cause at least some users*" to infringe, a court can "infer from [such] instructions an affirmative intent to infringe the patent." 633 F.3d at 60 (quoting *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009)) (emphasis added). This Court explained that the proposed label at issue in *Apotex* would "induce infringement because, absent instructions to the contrary," the label's instructions to "titrat[e] down to the lowest effective dose from the recommended starting dose of 2.5 mg of budesonide twice daily would necessarily *lead some users* to take 0.25 mg of budesonide once daily as a maintenance dose." *Id.* at 1055 (emphasis added).

Thus, the focus of the inducement inquiry in this cross-appeal is on whether Actavis's and West-Ward's labels "will cause at least some users" to prescribe or use Actavis's and West-Ward's tapentadol products in a manner that would infringe claims 1 and 2 of the '130 patent—to treat polyneuropathic pain.

B. Actavis's and West-Ward's Labels Will Cause a Large Number of Users to Use Their Tapentadol Products to Treat Polyneuropathic Pain

Here, Actavis and West-Ward will induce infringement of claims 1 and 2 of the '130 patent because the labels for their generic products contain an indication to use tapentadol to treat "severe chronic pain," which indisputably includes polyneuropathic pain. Thus, Actavis and West-Ward "will cause at least some users"—in fact, a large number of users—to use their tapentadol products for the treatment of polyneuropathic pain.

First, a drug's "indication" by definition instructs as to "its *intended* use or uses" that FDA has "approved" to be "safe and effective." *U.S. ex. rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613, 614 (2d Cir. 2016) (*citing, e.g.*, 21 U.S.C. § 355(a), (d), and *United States v. Caronia*, 703 F.3d 149, 152-53 (2d Cir. 2012)) (emphasis added). All of the experts agreed that an indication "provides specific instructions to doctors and physicians about the approved uses" of a drug. Appx10675 (99:44-7); *see also* Appx11891 (46:16-20); Appx9452-9453 (42:24-43:9); Appx9250 (229:15-18). Thus, the severe chronic pain indication instructs physicians,

pharmacists, and patients that the "intended use or uses" of Actavis's and West-Ward's products are for treating severe chronic pain, including all forms of such pain.

Second, all of the experts agreed that polyneuropathic pain is a common form of severe chronic pain. Appx9388-9389 (40:18-41:13, 41:19-23); Appx9399 (51:20-22); Appx9452-9453 (42:24-43:10); Appx9466-9467 (56:20-57:22); Appx9492 (82:4-9); Appx9482 (72:9-14); Appx10617 (41:9-11); Appx10675 (99:8-16); Appx9207 (186:21-23); Appx9247-9248 (226:23-227:8); Appx9009 (169:12-14); Appx9247 (226:23-25). As such, it was undisputed that the severe chronic pain indication *includes* polyneuropathic pain. Appx9482 (72:9-13); Appx9489 (79:9-17); Appx9490 (80:7-9); Appx10675 (99:8-16).

Third, it is undisputed that it would be readily apparent to physicians and other prescribers reading the severe chronic pain indication that the indication includes polyneuropathic pain, even though it may not explicitly use the words "polyneuropathic pain." Appx9498 (88:12:15); Appx10675 (99:8-16). This makes sense, as the "[t]arget audience" for these labels is "[p]rescribers," such as "[d]octors, nurse practitioners, [and] physicians assistants," who readily understand that the most common form of severe chronic pain is polyneuropathic pain. Appx11936 (91:4-8); Appx9250 (229:15-18). Indeed, this Court has acknowledged the importance of indications to this target audience, stating:

> [P]ersons of skill in the art look[] to drug labels, in part, for information about the use of the drug in special or specific populations, and that it is ***important*** for the [person of skill] ***to look at the label's indications section*** to see if a drug is indicated for administration to patients of certain characteristics with a certain intent.

Sanofi, 2017 WL 5180716, at *6 (citation and internal quotation marks omitted) (emphasis added).

Thus, the severe chronic pain indication in Actavis's and West-Ward's labels indisputably instructs the target audience that the "intended use or uses" of their products is the treatment of polyneuropathic pain. This would be readily apparent to at least physicians and other prescribers, who know that an indication instructs as to a product's "intended use or uses," and who know that polyneuropathic pain is a form of severe chronic pain. The labels therefore "will cause at least some users" to use and prescribe Actavis's and West-Ward's products in a manner that infringes claims 1 and 2 of the '130 patent: to treat polyneuropathic pain. Their "decision to proceed with [their] plan to distribute the [generic] drug despite being aware" from their own experts that "the label presented [these] infringement problems" only further confirms this conclusion. *See, e.g.*, *Apotex*, 633 F.3d at 1059-61.

C. The District Court Committed Several Legal and Factual Errors

The district court made several legal and factual errors in finding no inducement.

1. The court committed legal error when it concluded that Actavis's and West-Ward's labels would not "cause at least some users to infringe" because "doctors can and likely will follow the instructions on [their] label[s] to prescribe [the] product[s] for ***noninfringing purposes***." Appx166 (emphasis added); *see also id.* Appx168 (referring to "***[n]oninfringing uses*** of" Defendants' products) (emphasis added).

This Court has made clear that noninfringing uses are ***irrelevant*** to the induced infringement inquiry, and cannot preclude a finding of specific intent. *See, e.g.*, *Sanofi*, 2017 WL 5180716, at *7; *ERBE Elektromedizin GmbH v. Canady Tech. LLC*, 629 F.3d 1278, 1284 (Fed. Cir. 2010) (holding that there is no requirement "to prove that [an] accused product has no substantial non-infringing uses" "exists for induced infringement"); *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1364 (Fed. Cir. 2012) (citing *ERBE*, 629 F.3d at 1284) ("The existence of a substantial non-infringing use does not preclude a finding of inducement").

In *Sanofi*, the Court most recently explained that, including in the context of "drug labels," "there is ***no legal or logical basis*** for the suggested limitation [of substantial noninfringing uses] on inducement. Section 271(b), on inducement, ***does not contain*** the 'substantial noninfringing use' restriction of section 271(c), on contributory infringement." 2017 WL 5180716, at *7 (emphasis added). Thus, a defendant is "liable for inducing an infringing use of a product ***even if*** the product

has substantial noninfringing uses," which tapentadol does not. *Id.* (emphasis added). As such, this Court also "ha[s] not required evidence regarding the general prevalence of the induced activity" at issue to prove induced infringement. *Eli Lilly*, 845 F.3d at 1368–69.

Thus, the district court in this case committed legal error by focusing on whether physicians might prescribe Actavis's and West-Ward's products for severe chronic pain for a noninfringing purpose (*i.e.*, severe chronic pain that is not polyneuropathic in nature), which is irrelevant to a proper inducement inquiry. Here, the inducement inquiry asks only whether the labels "will cause at least some users" to use Actavis's and West-Ward's products to treat polyneuropathic pain, which is the most common form of severe chronic pain. *Apotex*, 633 F.3d at 1060. They unequivocally will.

2. The district court also incorrectly focused on whether Actavis and West-Ward "intend[] for [their] product to be used to treat *DPN*." Appx158-160 (emphasis added). By starting from that incorrect premise, the court concluded that "the fact that [Actavis and West-Ward] ha[ve] specifically carved out the DPN indication"—as opposed to the *severe chronic pain* indication—"is evidence that [they] do[] not specifically intend to encourage the use of the product for the treatment of DPN." Appx160.

That analysis is completely irrelevant. Claims 1 and 2 of the '130 patent, recite the treatment of polyneuropathic pain generally.[4] The claims are not limited to DPN, which is only *one type* of polyneuropathic pain. Thus, the district court's focus on whether Actavis's and West-Ward's labels instruct that the "intended use or uses" of their products include the treatment of *DPN* did not address the question as it applies to the labels at issue and the claims asserted. The labels at issue contain an indication instructing the use of tapentadol hydrochloride to treat "severe chronic pain," and the claims asserted cover all forms of polyneuropathic pain, which presents as severe chronic pain—about which all experts in this case agreed. Actavis and West-Ward's carve-out of the DPN indication has absolutely no bearing on whether their labels will "cause at least some users" to use the products to treat polyneuropathic pain and infringe claims 1 and 2.

3. The court further concluded that it would not be "readily apparent to [a] customer" reading "the label" that Actavis's and West-Wards' severe chronic pain indication instructs that the drug's "intended uses" includes polyneuropathic pain. Appx168 (emphasis added). But the court's conclusion directly contradicted the evidence and undisputed expert testimony that the "[t]arget audience" for these labels and indications are "[p]rescribers," such as "[d]octors, nurse practitioners,

[4] Other dependent claims of the '130 patent reciting the treatment of DPN were not asserted against Actavis and West-Ward.

[and] physicians assistants," who indisputably understand that severe chronic pain is a symptom commonly caused by polyneuropathic pain, and that an indication instructs as to a product's "intended use or uses." Appx9452-9453 (42:23-43:9); Appx9498 (88:12-15); Appx11935-11936 (90:24-91:8); Appx11981 (46:16-20); Appx10675 (99:8-16, 99:44-47); Appx9250 (229:15-18). Thus, it would be "readily apparent" to the "target audience" that the severe chronic pain indication is an instruction that the "intended use or uses" of Actavis's and West-Ward's products includes polyneuropathic pain. And as a result, the labels "will cause at least some users" to infringe.

4. Finally, the district court committed several errors in concluding that the treatment of polyneuropathic pain was "off-label" and by relying only on decisions involving off-label uses of a drug to reach its conclusion. Appx164-168. Those errors include the following:

First, the district court directly contradicted the undisputed expert testimony when it stated that the "treatment of polyneuropathic pain" was *not* "an on-label use of [Actavis's and West-Ward's] product[s]." Appx164. As discussed above, it was undisputed that polyneuropathic pain falls within the severe chronic pain indication, and thus the infringing use would squarely be an "on-label" use of Actavis's and West-Ward's products. Appx9482 (72:9-13); Appx9489 (79:9-17); Appx9490 (80:7-9); Appx10675 (99:8-16). The court cited to "Section IV.D.i.1.a.i" in its

opinion for support, but that section, as discussed above, incorrectly focused only on whether Actavis and West-Ward "intend[] for [their] product to be used to treat *DPN*" and whether DPN falls within the severe chronic pain indication—*not* whether *other types* of polyneuropathic pain fall within the indication. Appx158-160 (emphasis added).

Second, the district court misunderstood Plaintiffs' argument when it stated that "Plaintiffs cite no case law for the proposition that the mere fact that a use is on-label ends the inducement inquiry." Appx164-165. That was not Plaintiffs' argument. Rather, Plaintiffs explained that because the infringing use is indisputably contained within the indication of the label, the court need look no further to conclude that there will be induced infringement when physicians and pharmacists prescribe the drug for the indicated use. Plaintiffs made this distinction to explain why the cases upon which Actavis and West-Ward relied were "inapplicable," as they involved allegations of inducement for an off-label use of a drug. Appx17709-17710; Appx158-159 n.33 & 34. In those circumstances—which do not apply here—the patent holder must adduce some evidence to demonstrate that the off-label use is an intended use that will infringe the patent. This is a difficult hurdle to overcome, given that off-label uses are not approved uses by FDA. Here, however, Plaintiffs are not relying upon an off-label use to show inducement. On the contrary, it is the on-label use based on the express terms of the indication that establishes that

there will undeniably be induced infringement when physicians and pharmacists follow the indication's instructions in treating patients with severe chronic pain, which largely includes patients suffering from polyneuropathic pain.

* * * * *

Thus, for all of the foregoing reasons, the district court erred in concluding that Actavis and West-Ward would not induce infringement of claims 1 and 2 of the '130 patent.

II. The District Court Erred in Concluding That Actavis and West-Ward Would Not Contributorily Infringe the Asserted Claims of the '130 Patent

The district court concluded that there would be "substantial" noninfringing uses of Actavis's and West-Ward's products (*i.e.*, to treat the symptom of severe chronic pain that is *not* caused by polyneuropathic pain), despite the unrefuted evidence that the frequency of such uses would be ***rare***. The court therefore committed clear error in finding no contributory infringement.

A. The Substantial Noninfringing Uses Inquiry Is "Essentially a Quantitative One" That Considers the Frequency of Such Uses

A party is liable for contributory infringement if: (1) there is direct infringement; (2) the accused infringer knows of the patent at issue; (3) the product has no substantial noninfringing uses; and (4) the product is a material part of the invention. *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1320 (Fed. Cir. 2009). The district court's analysis focused on substantial noninfringing uses, as it

correctly held that Plaintiffs satisfied the three other factors. Appx173. This Court in *Vita-Mix Corporation v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009), stated that noninfringing uses can be "substantial" if they are "not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." Unfortunately, neither the district court nor the Defendants went any further in the requisite analysis.

After *Vita-Mix*, this Court clarified that "[w]hether a use is 'substantial,' rather than just [asking whether the use is] 'unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental,' cannot be evaluated in a vacuum," and should instead take into account the "use's ***frequency***," as well as its "practicality, the invention's intended purpose, and the intended market." *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010) (emphasis added).[5]

The substantial noninfringing use inquiry is "essentially a ***quantitative one***"; that is, "substantial non-infringing use can be shown when a '***significant number*** of [uses] would be non-infringing.'" *Pickholtz v. Rainbow Techs., Inc.*, 260 F. Supp. 980, 989 (N.D. Cal. 2003) (emphasis added) (quoting *Sony Corp. of Am. v. Universal Studios*, 464 U.S. 417, 442-43 (1984)). For instance, this Court in *C.R. Bard, Inc. v. Advanced Cardiovascular Systems, Inc.*, 911 F.2d 670, 674 (Fed. Cir. 1990),

[5] This Court has also recognized that *Vita-Mix* addressed a "non-pharmaceutical" scenario. *Sanofi*, 2017 WL 5180716, at *7.

considered evidence in the record that "40 to 60 percent" of the relevant uses were noninfringing to determine whether such noninfringing uses were "substantial."

Finally, once a patentee has "made out a *prima facie* showing" that a product is not "suitable for substantial non-infringing use," the "burden" then "shift[s]" ***to the accused infringer*** to demonstrate otherwise. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006).

B. The District Court Concluded That the Alleged Noninfringing Uses Were Substantial Even Though the Frequency of Such Uses Would Be *Rare*

The district court erred in confining its holding to the conclusion that the alleged noninfringing uses of Actavis's and West-Ward's tapentadol products would not be "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental," despite the unrefuted evidence that the "frequency" of such uses would be *rare*. Appx173-175; *i4i*, 598 F.3d at 851. Actavis and West-Ward argued at trial that their tapentadol products could be used to treat pain conditions not caused by polyneuropathic pain (*i.e.*, nociceptive, mononeuropathic), and thus would be noninfringing. Appx9225-9226 (204:14-206:21); Appx10582-10599 (6:12–23:25); Appx10619-10620 (43:24-44:11). Neither Actavis nor West-Ward presented any evidence regarding the frequency or rarity of such hypothetical events.

Plaintiffs presented *prima facie* evidence that the frequency of such noninfringing uses would be extremely *rare*—using tapentadol to treat purely

nociceptive or purely mononeuropathic pain conditions would be highly uncommon because such conditions rarely require "around-the-clock opioid treatment," as the label requires. Specifically, Plaintiffs presented unrefuted evidence that "less than 1%" of patients with some of the identified conditions and "less than 5%" of others were "due to purely nociceptive pain" or "mononeuropathic pain" *that was also* chronic, or required "around-the-clock opioid treatment." Appx11158-11159 (9:7-10:8); Appx11894 (49:2-7). Indeed, the minimal frequency of such uses could not possibly be considered "substantial" under its ordinary meaning in either the quantitative or qualitative context—"quantitatively large size" or "qualitative importance." *Life Techs. Corp. v. Promega Corp.*, 137 S. Ct. 734, 739-40 (2017) (interpreting the term "substantial" under 35 U.S.C. § 271(f)(2)).

Plaintiffs presented further evidence explaining why it would be rare to use tapentadol to treat purely nociceptive pain or mononeuropathic pain. Appx9471-9472 (61:22-62:12); Appx9486 (76:14-23). As an initial matter, polyneuropathic pain involves damages to the actual nerves (*i.e.*, spinal cord injury), and "nerves don't regenerate very well." Appx9388 (40:15-41:8). And because "neuropathic pain is very difficult to treat and" thus it is hard to "get it under control," it "typically will turn into a chronic pain." Appx9389 (41:9-13). Thus, polyneuropathic pain often requires "around-the-clock opioid treatment." *Id.*

On the other hand, nociceptive pain (*i.e.*, hitting your thumb with a hammer or cutting your hand with a knife) is "expect[ed] . . . to heal." Appx9388-9389 (40:15-41:8). As a result, nociceptive pain is "most often acute" rather than chronic, and it is therefore "typically . . . not treated with around the clock [medication]," and is treated "more with an as needed medication." Appx9472 (62:5-9); Appx9457 (47:9-14). Furthermore, treating mononeuropathic pain, whether it is severe and chronic or not, is rare because mononeuropathic pain, such as "diabetic mononeuropathy," is itself "very rare"—"polyneuropathic pain is far more common than mononeuropathic pain." Appx9457 (47:15-18); Appx9459 (49:4-10); Appx9472 (62:10-12).

Thus, the burden then shifted to Actavis and West-Ward to demonstrate that their alleged noninfringing uses *were* substantial, including that the frequency of such uses was *not* rare. Their experts, however, merely repeated *verbatim* the language from *Vita-Mix*, concluding that such uses would not be "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." 581 F.3d at 1327; *see, e.g.*, Appx9226-9227 (205:12-206:21). Actavis and West-Ward failed to offer *any* evidence as to the frequency of those uses, let alone evidence refuting Plaintiffs' evidence. Thus, Actavis and West-Ward failed to meet their burden of establishing that their alleged noninfringing uses would be substantial.

Accordingly, it was clear error for the district court to solely rely on Actavis's and West-Ward's conclusory testimony simply reciting the *Vita-Mix* language *verbatim* to conclude that the alleged noninfringing uses would be substantial. Appx75. The court's conclusion contravened this Court's clear instruction that the substantial noninfringing use inquiry takes into account more "than just" the *Vita-Mix* considerations (*i.e.*, unusual, far-fetched), such as whether the "frequency" of the noninfringing uses is "substantial." *i4i*, 598 F.3d at 851. In view of Plaintiffs' unrefuted evidence that the frequency of such uses would be minimal, Actavis's and West-Ward's noninfringing uses could not possibly be "substantial." As such, the court erred in finding no contributory infringement.

* * * * *

Thus, the district court committed clear error in concluding that Actavis and West-Ward will not induce infringement of or contributorily infringe claims 1 and 2 of the '130 patent. The district court's judgment of noninfringement as to Actavis and West-Ward should therefore be reversed.

CONCLUSION

The Court should affirm the district court's judgment that the asserted claims of the '130 patent are not invalid. The Court should reverse the district court's judgment that Actavis and West-Ward do not induce infringement or contributorily infringe claims 1 and 2 of the '130 patent.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Michael A. Sitzman, hereby certify that that I caused the foregoing to be filed via the Court's CM/ECF system and served on counsel of record who have registered for such service on December 1, 2017.

/s/ Michael A. Sitzman
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CERTIFICATE OF COMPLIANCE

The undersigned counsel certifies that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 16,448 words, excluding parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b). This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2016 in Times New Roman, 14-point.

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