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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REPLY 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: Cross-
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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:

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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

3/7/2018
Date

/s/ Michael A. Sitzman
Signature of counsel

Please Note: All questions must be answered

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Printed name of counsel

cc: All counsel of record via CM/ECF

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INTRODUCTION

Hidden beneath the array of arguments that West-Ward Pharmaceuticals International Limited and West-Ward Pharmaceuticals ("West-Ward") and Actavis Elizabeth LLC ("Actavis") (collectively, "Defendants") advance in response to Depomed, Inc.'s ("Depomed") cross-appeal is clear agreement as to the following undisputed facts and evidence necessary to decide whether Defendants infringe the '130 Patent:

(1) All experts at trial agreed that the indicated use on Defendants' proposed labels—using tapentadol to treat severe chronic pain requiring around-the-clock opioid treatment—includes treatment of polyneuropathic pain;

(2) The evidence at trial was undisputed that polyneuropathic pain is the *predominant* form of "pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate," as set forth in Defendants' proposed labels; and

(3) Defendants are seeking to market tapentadol to be used as their proposed labels instruct.

The only material disputes are legal ones. Does intentionally marketing a drug for its indicated and patented use constitute induced infringement, where rare noninfringing uses also fall within the indication? And does the existence of those rare noninfringing uses immunize the marketing of that drug from a finding of

contributory infringement? As Depomed explained in its opening brief, both this Court's case law and the plain meaning of 35 U.S.C. §§ 271(b) and (c) compel the conclusion that intentionally marketing a drug for a use that infringes, plus a relatively small number of noninfringing uses as well, constitutes both induced and contributory infringement. The district court committed legal error in concluding otherwise. This Court should therefore reverse the district court's judgment of noninfringement.

ARGUMENT

This Court gives independent review to the district court's legal errors, and will reverse if the district court has erred. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1123 (Fed. Cir. 2000). While infringement is ultimately a factual inquiry, it is one whose resolution can turn on legal issues—just as claim construction is a legal issue with underlying factual components. *See Phonometrics, Inc. v. N. Telecom Inc.*, 133 F.3d 1459, 1464 (Fed. Cir. 1998) (judgment as a matter of law proper where the "structure and operation of the accused devices" is not in "dispute"); *K-TEC, Inc. v. Vita-Mix Corp.*, 696 F.3d 1364, 1374 (Fed. Cir. 2012) (similar). It is these legal conclusions that the parties dispute, and which led the district court astray. Because "the district court erred in its interpretation of the infringement statute," and because "[t]his court reviews the

statutory construction of a district court *de novo*," the Court should reverse. *NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1314 (Fed. Cir. 2005).

I. Intentionally Marketing a Drug for an Infringing Use Constitutes Inducement Even if There Will Also Be a Small Number of Noninfringing Uses

The district court legally erred in construing 35 U.S.C. § 271(b). *See* Dkt. 81 ("DepomedBr.") 67-68. It held that, because "doctors can and likely will follow the instructions on [Defendants'] label[s] to prescribe [their] product[s] for noninfringing purposes," Defendants' actions did not fit within the scope of the inducement statute. Appx166. "But there is no legal or logical basis for the suggested limitation on inducement. . . . [a] person can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses." *Sanofi v. Watson Labs., Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017). And in this case, nearly all of the uses that fall within Defendants' labels will infringe the '130 Patent, as Defendants well know. Such intentional promotion of infringement is inducement under the statute. *See Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 761 (2011).

A. Defendants' Labels Induce Infringement by Encouraging Doctors to Infringe

Defendants' labels will "encourage[] . . . administration of the drug to [polyneuropathic-pain-suffering] patients, thereby causing infringement." *Sanofi*, 875 F.3d at 645. Defendants seek approval to market tapentadol for the indication

"pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate" (Dkt. 95 ("ActavisBr.") 24; Appx52876) or "moderate to severe chronic pain in adults . . . when a continuous, around-the-clock opioid analgesic is needed for an extended period of time" (Appx56114 (West-Ward label)). All the experts—even Defendants' experts—agree that such pain includes, predominantly, polyneuropathic pain. Because treating polyneuropathic pain fits squarely within the terms of Defendants' respective labels, Defendants induce infringement of the '130 Patent.

Defendants *concede* the crucial facts which compel that conclusion. Defendants do not deny that polyneuropathic pain is a common type of severe chronic pain. Instead, they argue it is "irrelevant" that "physicians might understand 'severe chronic pain' to encompass polyneuropathic pain." Dkt. 96 ("West-WardBr.") 38-39; *id.* at 48 (similar); ActavisBr. 27 ("At most, Plaintiffs presented evidence indicating that, because polyneuropathic pain is a type of severe chronic pain, Actavis's label *permits* infringement."). Nor do Defendants dispute that polyneuropathic pain is, in fact, the most common type of "severe" or "chronic" pain requiring "around-the-clock" treatment. Appx52876; Appx56114. It necessarily follows that treating polyneuropathic pain around-the-clock with tapentadol would be the primary on-label use. *See* Appx10675 (Defendants' expert admitting that the label "would include patients with polyneuropathic pain"); Appx9248 (Defendants'

expert admitting that "physicians might use" "Actavis' generic product" for "treatment of neuropathic pain"); Part II, *infra*.

Inducement liability follows as a matter of law and logic. That the indication section of Defendants' labels encompass the use of tapentadol hydrochloride to treat polyneuropathic pain *means* that Defendants are seeking to market tapentadol hydrochloride for use in treating polyneuropathic pain. Using tapentadol hydrochloride to treat polyneuropathic pain infringes claims 1 and 2 of the '130 Patent. Defendants therefore are seeking to market an infringing on-label use. That is the *sine qua non* of inducement. *See Sanofi*, 875 F.3d at 645; *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1059-60 (Fed. Cir. 2010). "As the Supreme Court explained in *Grokster* in the context of infringement under the copyright laws, 'evidence of active steps . . . taken to encourage direct infringement, such as advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe.'" *AstraZeneca*, 633 F.3d at 1059 (quoting *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005)).

AstraZeneca and *Sanofi* are controlling here; and, under these precedents, Defendants infringe. Like the defendant in *AstraZeneca*, Defendants here "included instructions in [their] proposed label[s] that will cause at least some users to infringe the asserted method claims." *Id.* at 1060. Defendants' labels "would inevitably lead

some consumers to practice the claimed method" because, like the label in *Astra-Zeneca*, many of the treatments encompassed by the label would infringe—and Defendants have not revised their labels to exclude such infringing treatments (such as by indicating that the drug may only be used to treat nociceptive or mononeuropathic pain or both). *Id.*; *see* West-WardBr. 42-43 (noting these features of *AstraZeneca*); ActavisBr. 23 (same). Therefore, the label encourages infringement. *AstraZeneca*, 633 F.3d at 1059-60.

Indeed, as was the case in *Sanofi*, where "[a]pproximately 77% of [the] prescriptions ha[d] actually been written for patients with the claimed risk factors" (875 F.3d at 645), here there is evidence that the *large majority* of on-label uses—those falling within Indication 1—will be infringing (Part II, *infra*). Given this undisputed fact, it does not matter whether tapentadol "has substantial noninfringing uses not forbidden by the proposed labels." *Id.* at 646. The existence of noninfringing uses is immaterial to inducement for many reasons. Not only does Section 271(b) lack the "substantial noninfringing use" language found in Section 271(c), "the core holding of *Grokster*, a copyright decision that drew expressly on patent and other inducement law, is precisely that a person can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses." *Id.* (citing *Grokster*, 545 U.S. at 934-37); *accord*, *e.g.*, *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1364 (Fed. Cir. 2012).

While it is true that a defendant must intend to induce some users to infringe before it may be held liable for inducement, that intent is amply supplied when the defendant is seeking to market a drug for a broad purpose, the vast majority of which is infringing. A drug's "indication," by definition, instructs the "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). Although permission is not necessarily encouragement, *marketing* a drug for a labelled use is encouragement of that use, not permission. *See AstraZeneca*, 633 F.3d at 1059; *Sanofi*, 875 F.3d at 646.

West-Ward argues that "the factual record here" does not demonstrate that it is seeking to market tapentadol for the indicated use. West-WardBr. 47. But this Court's case law is clear that the ANDA alone supplies that intent under 35 U.S.C. § 271(e)(2). Depending on what the label instructs, "the decision to continue seeking FDA approval of those instructions may be sufficient evidence of specific intent to induce infringement." *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 845 F.3d 1357, 1368 (Fed. Cir. 2017). If the proposed label is for "a use *not* covered by the patent[]," then the ANDA does not show intent to induce; by contrast, "a label that instruct[s] users to follow the instructions in an infringing manner [i]s sufficient even though some users would not follow the instructions." *Id.* at 1368-69 (emphasis added). The latter is the case here; the label instructs that tapentadol be

used an infringing manner—for the treatment of polyneuropathic pain. Thus, "[t]he content of the label in this case permits the inference of specific intent to encourage the infringing use." *Sanofi*, 875 F.3d at 646.

B. Defendants' Labels Instruct Practitioners to Use Tapentadol in an Infringing Manner

As explained above, health care providers will see, read, and understand Defendants' labels as instructing them to use tapentadol to treat polyneuropathic pain—*i.e.*, to infringe the '130 Patent. Defendants do not dispute this fact; instead they argue that the Court should ignore it. None of their reasons for doing so withstands scrutiny.

First, West-Ward argues that the Court must ignore "physicians' independent knowledge of pain treatments from *outside* the label." West-WardBr. 40, 44-45. That gets the law completely backwards.[1] A defendant induces infringement if it "persuade[s] another to engage in conduct that the inducer knows is infringement." *Global-Tech*, 563 U.S. at 761. The Court accordingly must consider *what conduct* the defendant is promoting. If the defendant and the doctor would understand that

[1] West-Ward's argument is especially curious given that West-Ward notes that "the proper inducement analysis . . . allows considerations of affirmative evidence outside the final label to show that intent is *lacking*." West-WardBr. 53 (emphasis added). There is no reason—and certainly none consistent with due process—why evidence from outside the label may be considered only to negate intent, not to show it.

the defendant is asking the doctor to use tapentadol hydrochloride to treat polyneuropathic pain, knowing that to be infringing, then the defendant is inducing infringement of claims 1 and 2 of the '130 Patent. *See Sanofi*, 875 F.3d at 645 (finding inducement because "a physician would find 'clear encouragement' from the label to use dronedarone in a manner that infringes the '167 patent"). Here, there is no dispute that Defendants know that using tapentadol to treat polyneuropathic pain directly infringes. And there is no dispute that a physician would read the label as instructing that use.

In determining whether the label encourages a physician to engage in an infringing activity, the trier of fact may not ignore a physician's background knowledge about, for example, which conditions require around-the-clock pain treatment. *Cf. Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (trier of fact must "account for critical background" "knowledge and perspective of one of ordinary skill in the art" in determining validity). In arguing that the Court must ignore how a doctor would read the label, West-Ward seriously misinterprets this Court's decision in *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625 (Fed. Cir. 2015). *Takeda* held that, to find inducement, "[t]he label must encourage, recommend, or promote infringement." *Id.* at 631. As a result, the patentee must show that a physician would read the *indication* as including an infringing use; it is not enough that the label asks the patient to "tell your healthcare

provider" about other conditions. *Id.* at 632. Here, physicians would read the indication in Defendants' labels—using tapentadol to treat severe chronic pain requiring around-the-clock treatment—as encouraging the use of tapentadol to treat polyneuropathic pain. To arrive at this straightforward reading, physicians do not need to consult any text outside the label or wait for patients to ask about other conditions, as would be required in an *off-label* case like *Takeda.* As in *Sanofi* and "[u]nlike in *Takeda*, the inference in the present case is based on interpreting the label's express statement of indications of use"—not evidence outside the label. *Sanofi*, 875 F.3d at 646.

Second, Actavis notes that the scientific community has debated the use of opioids *in general* to treat neuropathic pain. ActavisBr. 14-15, 25-27. But this fact says nothing about how a doctor would *today* read a label for *tapentadol*. Depomed and Grünenthal GmbH (collectively, "Plaintiffs") have now developed tapentadol and shown that, contrary to expectations that opioids *in general* will not effectively treat neuropathic pain, tapentadol *specifically* is effective for treating polyneuropathic pain. *See* DepomedBr. 10-17. Indeed, it is undisputed that tapentadol is the *only* opioid FDA has ever approved for treatment of polyneuropathic pain. *See* DepomedBr. 18. Defendants' generic tapentadol will be prescribed long *after* the scientific community (including FDA) recognized that tapentadol effectively treats polyneuropathic pain. Clinicians will not forget this fact

when prescribing tapentadol;[2] Defendants will not forget it when marketing their drugs; and the Court is not required to forget it when deciding this case.

Third, for similar reasons, there is no "tension" in reading the term "pain" in U.S. Patent Nos. RE39,593 and 6,248,737 (of which No. RE39,593 is a reissue) (together, the "Compound Patent") as referring only to nociceptive pain. *Contra* ActavisBr. 13-14, 26-27. The Compound Patent—as compared to Defendants' labels—is an entirely different document, directed to a different audience, at a different point in time than the doctors who will prescribe generic tapentadol to their patients well after the Compound Patent expires in 2022. The Compound Patent addresses those of skill in the art in drug development in 1994, long *before* the

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[2] As Plaintiffs' expert, Dr. Michelle Brown, explained, clinicians would not forget that studies have shown tapentadol effective for treating polyneuropathic conditions when reading Defendants' labels. Appx11861-11862; Appx11871-11872; Appx11886. Contrary to Actavis's argument (at 32) that there is something impermissible about Dr. Brown consulting her knowledge of tapentadol's uses, the evidence is a clinician would read the label just as she would. Defendants also conclusorily claim that "a physician reading the label would not understand that the product had been shown to be effective in treating neuropathic pain." ActavisBr. 25; *accord* West-WardBr. 45. But Defendants cite only their experts' statements that the label "does not *specifically* instruct the physician to prescribe it for polyneuropathic pain" (Appx10676 (emphasis added)) and, equivalently, that the label has no "specific instruction" or "directions about using it for neuropathic pain" *specifically* (Appx9207-9208). This says nothing about whether a clinician would read the label as an instruction to use tapentadol to treat certain types of pain, *including* polyneuropathic pain, which Defendants' experts admitted was included in the label's instructions (*e.g.*, Appx9207; Appx10675).

formulation of NUCYNTA® ER and before the discovery that tapentadol was effective in treating polyneuropathic pain, when *all* opioids were understood to treat nociceptive pain only.

The Compound Patent also delivers a very different message from Defendants' labels. The Compound Patent generally refers to treating "pain." *See* DepomedBr. 35-41. By contrast, Defendants' labels refer to patients suffering from severe chronic pain needing "around-the-clock" treatment—a notion absent from the Compound Patent. As is undisputed, pain patients requiring around-the-clock treatment overwhelmingly suffer from *neuropathic* pain. *See* DepomedBr. 8-9, 23, 74-76. It is also undisputed that virtually all of this neuropathic pain would be polyneuropathic, because it is very rare that only one nerve suffers damage (the definition of "mononeuropathic pain"). *See* DepomedBr. 9, 22-23, 76. Thus, "a physician would find 'clear encouragement' from the label to use [tapentadol] in a manner that infringes the '[130] patent," regardless of what drug developers would find from reading the Compound Patent in 1994. *Sanofi*, 875 F.3d at 645. Depomed's argument that Defendants have not proven invalidity of the '130 Patent in view of the Compound Patent by clear and convincing evidence does not contradict its argument that Plaintiffs have proven infringement of the '130 Patent by a preponderance of the evidence. *See* DepomedBr. 62-63.

Finally, Actavis argues that the fact that it stipulated to infringement of claim 8 of the Compound Patent somehow means that it cannot infringe the '130 Patent. ActavisBr. 30, 36. The stipulation neither says, nor implies, anything of the sort. Indeed, the stipulation does not say *how* Actavis infringes the '593 Patent. Appx7771. A single label can infringe multiple patents covering treatment of different diseases—for example, by inducing treatment of multiple different categories of the labelled use. Here, Actavis's label can induce both treatment of nociceptive pain and treatment of polyneuropathic pain—both of which are covered by its label.

C. Defendants Cannot Escape Inducement Liability by Carving Out One Example of Polyneuropathic Pain

Even though Defendants' label encompasses treatment of polyneuropathic pain, Defendants argue that they should be immunized from inducement liability because, rather than copying both indications in Depomed's current label, Defendants carved out the indication for diabetic peripheral neuropathy (DPN) (Indication 2) and references to neuropathic pain *associated with DPN*. *See* West-WardBr. 48, 50, 53; ActavisBr. 24. But Defendants left in the indication for severe chronic pain requiring around-the-clock treatment, which indisputably and predominantly includes treatment of polyneuropathic pain. Defendants ask the Court to simply ignore what is being encouraged and instructed by Indication 1, and

to focus only on the fact that they carved out the DPN indication and references to neuropathic pain associated with DPN.

Defendants' "efforts to avoid the use of *the term* 'polyneuropathic pain' in [their] label[s]" (ActavisBr. 2 (emphasis added)) do not avoid *encouraging infringement*. The only references that Defendants removed from their label were explicit mentions of *DPN*; Defendants carved out the DPN indication and references to *neuropathic pain associated with DPN*. *See* DepomedBr. 20. The removal of the DPN indication and references thereto does nothing to countermand Indication 1's instruction to prescribe tapentadol to treat severe, chronic pain in patients requiring around-the-clock treatment—including polyneuropathic pain.

Indeed, Defendants' conduct in this regard is *evidence* of intent to induce infringement. *See Global-Tech*, 563 U.S. at 770-71 (defendant's efforts to avoid knowledge satisfied the intent-to-induce element). Erasing from the label one particular form of polyneuropathic pain, while retaining broader words that encompass all forms of polyneuropathic pain, cannot prove noninfringement. As West-Ward acknowledges, it "is hardly debatable" that "'magic words' in the label matching the language of the patent are not required for a finding of inducement." West-WardBr. 51.

West-Ward argues that, if Depomed were correct, then there would have been no need for Depomed's predecessor-in-interest Janssen to obtain Indication 2 in

2012. West-WardBr. 46-47. This argument conflates patent law with FDA regulations and fails to account for the "severe" consequences a company can face when it deviates from the *ipsissimis verbis* indication and markets more specific conditions. *See* 2 Food and Drug Admin. § 15:63 (2017). Indeed, in 2014, FDA issued a Warning Letter to at least one company for marketing a drug *for conditions encompassed by its indication* but different than the specific conditions described in the studies on the label. *See* Complaint, *Pacira Pharm., Inc. v. FDA*, No. 1:15-cv-07055, 2015 WL 5256628 (S.D.N.Y. Sept. 8, 2015). The Warning Letter triggered an 11% drop in the drug maker's stock price and civil litigation. *See Lovallo v. Pacira Pharm., Inc.*, No. CV-14-06172-WHW, 2015 WL 7300492, at *3 (D.N.J. Nov. 18, 2015). Even though FDA eventually rescinded the letter and concluded that the marketing was permissible all along (after the drug maker sued the agency),[3] Janssen's decision to obtain a DPN-specific indication came long before FDA's

[3] *See* Marisa A. Trasatti and Marie Claire Langlois, *Feds, Pharma, and Free Speech*, 59 No. 1 DRI For Def. 10 (2017); *Pacira and FDA Resolve Warning Letter Squabble Out of Court*, 23 No. 12, FDA Advertising & Promotion Manual News. 1 (Feb. 2016); FDA, Letter to Pacira (Dec. 14, 2015), available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/enforcementactivitiesbyfda/warninglettersandnoticeofviolationletterstopharmaceuticalcompanies/ucm477250.pdf.

change of heart. Obtaining Indication 2 may have proven supererogatory[4]—but, based on regulatory policy at the time, it presented a prudent and cautious course. As a witness from Janssen testified at trial, Janssen *never* believed that it "needed to have a second indication for neuropathic pain associated with DPN in order for the treatment of DPN to be on label"; Janssen obtained Indication 2 in an abundance of caution, to ensure that FDA would regard DPN treatment as "promotable." Appx8967 (127:8-22).

In this context, the internal Janssen document Actavis cites does not show that polyneuropathic pain, or DPN specifically, is off-label. *See* ActavisBr. 33. It merely indicates that providers were prescribing tapentadol for conditions beyond the "chronic low back pain" that was the subject of one of the studies mentioned in the label. *Id.* In any event, this internal document says little about what *a physician* would read from the label.

West-Ward also argues that Indication 1 cannot encompass DPN because Plaintiffs do not assert the DPN-specific claims in the '130 Patent against West-

[4] The upshot of Defendants' argument is that Janssen should not have performed and disclosed the studies supporting Indication 2; by doing so, Defendants argue, Janssen forfeited its right under the '130 Patent to exclude generic manufacturers. Adopting Defendants' argument would discourage biomedical and pharmaceutical companies from engaging in and publicizing beneficial research, and from obtaining approval for specific uses already encompassed within a general indication. It would impede the progress of science and the useful arts.

Ward, even though they have done so against Alkem, whose label includes the DPN-specific indication. West-WardBr. 47. Plaintiffs' decision to avoid argument over the DPN-specific dependent claims in the face of a section viii carve-out, and thereby to conserve judicial and parties' resources, is not evidence of noninfringement. Plaintiffs recognized there would be no point to engage West-Ward in litigation about the narrower claims, when West-Ward clearly infringes the broader claims and they are valid for much the same reasons as the narrower claims.

In short, Indication 2 is an irrelevant and immaterial distraction from Depomed's infringement allegations against West-Ward and Actavis. Defendants will market tapentadol per Indication 1, a broad indication that includes infringing uses and almost no *non*infringing uses. If Defendants truly intended *not* to encourage infringement of the '130 Patent, they had options. They can of course wait until the patent expires. Or, as Dr. Brown explained, they could have added to the "Limitations of Use" section of their labels an instruction *not* to prescribe the drug for polyneuropathic pain—or to prescribe it *only* for nociceptive and mononeuropathic pain. Appx11889; Appx11937. Instead, Defendants are seeking to market tapentadol for infringing uses encompassed by Indication 1. The district court legally erred in concluding that this is not inducement. *See Sanofi*, 875 F.3d at 646 ("The evidence in this case supports the finding of intentional encouragement of infringing use and, therefore, of inducement.").

II. The Rare, Noninfringing Use of Defendants' Products Does Not Exculpate Defendants' Contributory Infringement

The district court also legally erred in concluding that the "very uncommon" use of tapentadol to treat *non*-polyneuropathic pain precludes a finding of contributory infringement. Appx175. In reaching this conclusion, the court correctly recognized that "a substantial non-infringing use must be one for which the product is authorized to be sold—*i.e.*, it must be on label." Appx173 (citing *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 927 (Fed. Cir. 2011)). But while the court stated this legal principle correctly, it failed to analyze (1) whether the non-infringing use proffered by Defendants was indeed on-label, and, if so, (2) whether it was a "substantial" part of on-label use. These failings are critical because off-label, "unauthorized activity does not avoid infringement" (*Eli Lilly*, 435 F. App'x at 927); only "substantial *lawful* use" counts in the contributory infringement analysis (*Grokster*, 545 U.S. at 932-34 (emphasis added)).

Plaintiffs presented copious, uncontradicted evidence that on-label noninfringing use in this case would be rare at best. *See* DepomedBr. 8-9, 22-23, 75-76 (citing, *e.g.*, Appx11894). In its decision, the district court recounted that "most conditions that present severe chronic pain, and are thus on-label for Defendants' products, are polyneuropathic in nature." Appx174. The court also noted that Defendants had offered evidence of non-polyneuropathic conditions that could be treated with tapentadol, but that Plaintiffs had shown that practically all of

Defendants' purported noninfringing uses were for *acute* pain, not chronic pain as required by the label. Appx174-175. As for those conditions that fall within the label *and that are not polyneuropathic*, those conditions are rare: The court recited Plaintiffs' *uncontradicted* evidence that "less than 5%" of patients "suffer[] from purely nociceptive or mononeuropathic components of the *Defendants'* identified conditions." Appx175 (emphasis added). In addition, as Depomed explained in its opening brief, purely nociceptive or mononeuropathic pain seldom requires around-the-clock treatment as required by the label. Thus, the frequency of any noninfringing on label use would be extremely rare. *See* DepomedBr. 8-9, 22-23, 75-76.

In short, the district court and the parties agree that on-label noninfringing uses are *possible*, but neither the district court nor Defendants cite anything contradicting the undisputed evidence that such uses are *rare*. The only question presented is the legal conclusion that follows therefrom. The district court concluded that as long as there was a single on-label noninfringing use that was not "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental," that use is "substantial" within the meaning of the statute. Appx175. Under the plain meaning of "substantial noninfringing use" and this Court's precedent, the district court committed clear legal error.

A. Rare Noninfringing Uses Are Not "Substantial" Within the Meaning of Section 271(c)

Rather than challenge the evidence establishing that noninfringing on-label uses would be *rare*, Defendants argued that noninfringing uses were simply *possible*. *See* West-WardBr. 55-56, 59-60; ActavisBr. 34 (citing Appx9225 (Defendants' expert testifying that certain conditions "*might* be caused by" non-polyneuropathic mechanisms and "*may* cause severe pain and require daily around-the-clock dosing" (emphasis added))).[5] At its heart, Defendants' position boils down to the legal contention that, so long as there is a single noninfringing use that is not "impractical," "aberrant," nor "experimental," there can be no liability for contributory infringement. *See*, *e.g.*, West-WardBr. 56 ("An on-label use for an accused drug product . . . *simply cannot be* 'impractical,' 'aberrant,' or 'experimental'" (emphasis added)). In other words, Defendants argue, no matter

[5] The evidence cited by West-Ward is to the same effect. West-Ward also relies on "demonstrative exhibits," which "are not evidence at all" (*Baugh v. Cuprum S.A. de C.V.*, 730. F.3d 701, 707 n.1 (7th Cir. 2013)) and were not admitted into evidence here (Appx59 n.7). The demonstratives and accompanying discussion on which West-Ward relies list a variety of supposedly noninfringing conditions. Appx9225-9228. But cross-examination revealed that these conditions are *acute* and thus *off-label*. Appx10684-10688. If the Court does consider Defendants' demonstratives, it should also consider Plaintiffs' demonstratives illustrating this fact. Appx64273-64280. West-Ward also cites its own Proposed Findings, which are "not evidence" (*Orson, Inc. v. Miramax Film Corp.*, 79 F.3d 1358, 1367 n.9 (3d Cir. 1996)) and may not be "incorporated" into West-Ward's brief on appeal (*Norman v. Elkin*, 860 F.3d 111, 130 n.26 (3d Cir. 2017)).

how rare the use may be, so long as there is *some* noninfringing use, they cannot be found to contributorily infringe the '130 Patent.

That is not the law. A single on-label use is not substantial; to hold otherwise would be to write "substantial" out of the statute and allow *any possible* lawful noninfringing use to excuse infringement. The statute is clear: An article must have "substantial" noninfringing uses if its role in infringement is to be excused. 35 U.S.C. § 271(c). Whether a use is substantial is a relative inquiry. Noninfringing on-label uses must be "substantial" in relation to the on-label uses as a whole. *See* DepomedBr. 73-75. Indeed, there is no way to determine whether a use is "substantial" except in relation to other on-label uses. As courts have recognized in other contexts, "the term 'substantial' is a relative one. Its meaning rests on an implied comparison between the described subject and a larger unit, just as the expression 'a substantial saving,' suggests that the saving is 'substantial' in comparison with the value of the item purchased." *Heft v. C.I.R.*, 294 F.2d 795, 797 (5th Cir. 1961).

Defendants—like their experts—have little argument against this principle of law and logic, except to parrot the string of adjectives originating in *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009): "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." West-WardBr. 57-58; ActavisBr. 37; Appx10619-10620 (Defendants' expert basing his conclusion on the

"understanding" that "the definition of . . . substantial non infringing use" is uses that "are not unusual, far-fetched, illusory or impractical, occasional, aberrant or experimental").

But Defendants do not grapple with this Court's subsequent clarification that "[w]hether a use is 'substantial,' rather than just 'unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental,' *cannot be evaluated in a vacuum*." *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010) (quoting *Vita-Mix*, 581 F.3d at 1327) (emphasis added). Actavis conspicuously ignores *i4i*. West-Ward notes that *i4i* permitted the factfinder to consider the use's frequency, but omits its holding that whether a use is substantial "cannot" be evaluated without reference to other uses, as Defendants would have the Court do. West-WardBr. 58.

Contrary to West-Ward's suggestion (at 57), this Court's subsequent decision in *Toshiba* did not somehow abrogate *i4i*: Immediately after reciting the *Vita-Mix* adjectives, the *Toshiba* Court noted that the inquiry is informed by, among other things, "the use's frequency." 681 F.3d at 1362 (quoting *i4i*, 598 F.3d at 851). The Court affirmed the finding of noninfringement because the patentee "presented no survey, expert, or other evidence showing how frequently users" engage in the

noninfringing use.[6] *Id.* at 1363. *Toshiba* thus reaffirms that the substantiality inquiry focuses on the frequency of the alleged noninfringing use.

In any event, Defendants apparently agree that a use is insubstantial if it is "unusual" or "occasional." West-WardBr. 54, 57; ActavisBr. 34, 37. As explained below, any on-label noninfringing use of Defendants' products will be an unusual use—an uncommon way of using tapentadol according to its label.

B. Defendants Do Not Deny That Any Noninfringing On-Label Use of Their Products Would Be Rare

Defendants point to no evidence challenging the fact that any *on-label* noninfringing use would be rare. They say nothing to dispute the only quantifiable evidence of the frequency with which an on-label use is noninfringing: the evidence acknowledged by the district court that "less than 5%" of patients "suffer[] from purely nociceptive or mononeuropathic components of the Defendants' identified conditions." Appx175 (emphasis added). In other words, even for the conditions that *Defendants* claim present noninfringing uses, the only evidence is that over 95% of the patients taking tapentadol will be treated for polyneuropathic pain—*i.e.*, over

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[6] Defendants' other case, *In re Bill of Lading Transmission & Processing Sys. Patent Litig.*, 681 F.3d 1323 (Fed. Cir. 2012), is completely inapplicable given that the *substantiality* of any noninfringing use was not even at issue. *Id.* at 1338 (holding that a complaint alleging that an item was incapable of noninfringing uses *when it is used in an infringing way* did not state a claim for contributory infringement).

95% of the uses of tapentadol are actually infringing. Still further, Depomed's opening brief collects copious evidence that even for the conditions *Defendants* believe are noninfringing, only a miniscule percentage require treatment of patients needing around-the-clock administration of opioids as set forth in the tapentadol label. *See* DepomedBr. 8-9, 22-23, 75-76 (citing, *e.g.*, Appx11894).

Because Defendants did not proffer any evidence to contradict these numbers, West-Ward notes that Depomed also offered *additional* evidence that chronic pain is "often" neuropathic and argues that "often" is not sufficiently specific. West-WardBr. 60. Incredibly, West-Ward argues that "without absolute numbers," there is no way of knowing "the relative frequency of *noninfringing versus infringing uses*." *Id.* While that may be true, *Plaintiffs* were the only ones that supplied the pertinent "numbers," and the only numbers cited by the district court were Plaintiffs'. Appx175.

Defendants also point to a hodgepodge of statements and recitations concerning chronic lower back pain, none of which address the pertinent question, namely: What fraction of on-label uses are noninfringing? West-Ward, for example, cites contradictory figures about the components of chronic lower back pain. West-WardBr. 59-60. But none of these numbers were credited by the district court. Clear error review cannot apply to a determination the district court never made based on

evidence it did not credit. *See WundaFormer, LLC v. Flex Studios, Inc.*, 680 F. App'x 925, 930 (Fed. Cir. 2017).

In any event, West-Ward's numbers do not indicate whether *on-label* noninfringement is common or not. In particular, they do not address the "severe" or "around-the-clock" limitations in Defendants' labels. *See*, *e.g.*, Appx9508 ("The sentence that you have highlighted does not discuss anything about the severity of the chronic low back pain."); Appx9512 ("It doesn't specify whether pain is severe."). Rather, West-Ward's numbers concern *all* patients suffering from lower back pain, not the subset of such patients who may be treated according to Defendants' labels: those requiring "around-the-clock" treatment. The *only* evidence to that point shows that patients requiring around-the-clock treatment typically suffer from polyneuropathic pain. *See* DepomedBr. 8, 22-23, 75 (citing evidence).

In addition, West-Ward's lower-back-pain figures do not concern any other condition—or show the relative frequency of lower back pain compared to other conditions that might require treatment with tapentadol. *See* Appx11894 (five percent "[o]f the chronic low back pain patients" would fall within Defendants' labels and have pain of nociceptive origin, "[b]ut that's not everybody that would fall under the indication").

Actavis adds that "rheumatoid arthritis and osteoarthritis" can "cause chronic and severe nociceptive pain." ActavisBr. 11-12, 34. But this says nothing about whether these conditions *also* cause polyneuropathic pain, as covered by the '130 Patent. *All* treatment of polyneuropathic pain using tapentadol hydrochloride is infringing, even if the administration of tapentadol *also* treats mononeuropathic or nociceptive pain at the same time. This evidence therefore does not answer whether treatment of these conditions is infringing. And like West-Ward's evidence, it says nothing about whether such treatment would be *on-label*, because it does not address patients in need of *around-the-clock* treatment.[7]

Given the lack of evidence supporting its contention, Actavis attempts to impugn the credibility of Plaintiffs' expert, Dr. Brown. ActavisBr. 32. But the district court did not find Dr. Brown's testimony non-credible; it repeatedly cited and relied on her testimony. Appx174-175. And Actavis does not dispute that the figures she provided are the only actual numbers in evidence. Even if Dr. Brown's "testimony was not credited by the district court"—which it was—"that fact cannot

[7] Indeed, Actavis is wrong that its experts gave even a subjective impression—much less specific numbers—about the proportion of on-label use that is noninfringing. Actavis says its experts "testified that the non-infringing uses would be 'common.'" ActavisBr. 35, 37. The quoted passage actually says that two *conditions* are "common" in the *patient population*—not that these are common sources of non-polyneuropathic pain in people needing around-the-clock tapentadol treatment. Appx10683.

be used as affirmative evidence of the opposite conclusion." *1st Media, LLC v. Elec. Arts, Inc.*, 694 F.3d 1367, 1376 (Fed. Cir. 2012). To the extent the district court can be read as relying on Dr. Brown's supposed lack of credibility as evidence that on-label noninfringing uses were common, that "finding is clearly erroneous." *Id.*

Actavis also attempts to twist Dr. Brown's statement that 40 to 50 percent of her patients experience polyneuropathic pain into some sort of "admi[ssion]." ActavisBr. 35. But this statement concerned Dr. Brown's entire "patient population," *not* "what percent [she] treat[s] with opioids." Appx11182. Much less did it concern the specific patients that Defendants' drugs are indicated to treat, namely patients who: (1) are treated with tapentadol hydrochloride, (2) require around-the-clock treatment, and (3) experience severe chronic pain. As Dr. Brown explained, "the denominator of the fraction is extremely important"—and Defendants' figures use the wrong denominator. *Id.*

The evidence points to only one conclusion, which no one disputes: Noninfringing uses may exist, but they would be rare. Because rare noninfringing uses are not "substantial," the district court legally erred in concluding that there are substantial noninfringing uses of Defendants' products.

C. The District Court Correctly Found that Defendants' Products Constitute a Material Part of the Invention, Especially Adapted for Infringing Use

Defendants' final argument is a throwaway, and can be disposed of as such. As the district court noted, contributory infringement requires "1) that there is direct infringement, 2) that the accused infringer had knowledge of the patent, 3) that the component has no substantial noninfringing uses, and 4) that the component is a material part of the invention." *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010) (cited at Appx172-173). Defendants, for the first time on appeal, argue that the fourth element is lacking. West-WardBr. 61-62; ActavisBr. 37-38. Yet the district court found that "each Defendant's tapentadol hydrochloride product is a material part of the invention." Appx173. The court also noted that Defendants had not disputed this element at trial. *Id.*

Defendants now argue on appeal that the district court omitted from its analysis that the product must be a material part of the invention, *especially adapted for infringing use*. West-WardBr. 61-62; ActavisBr. 37-38. Defendants apparently blame the district court for not parroting these exact words and instead using the shorthand "material part of the invention." But the district court can hardly be faulted for using *the same shorthand* this Court used in *Fujitsu*, especially when all that needed to be said is that Defendants did not deny the existence of this element. Indeed, conspicuously absent from Defendants' argument is any citation to any place

in the trial record where Defendants disputed this element or proffered evidence of the contrary. This Court should not disturb the district court's finding that Defendants have abandoned any such dispute. *See MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1271 (Fed. Cir. 2013) (defendants "waived the issue of indefiniteness by failing to raise it at the bench trial").

Regardless, it is abundantly clear that Defendants' generic version of NUCYNTA® ER *is* especially made for treating polyneuropathic pain. The '130 Patent itself highlights that tapentadol is uniquely suited among opioids for this very purpose; this surprising and unexpected discovery resulted in the '130 Patent being granted. Notably, NUCYNTA® ER was the first and only opioid ever approved for the treatment of polyneuropathic pain. *See* DepomedBr. 10-17, 45-61.

Finally, just as Defendants argue that their evidence about tapentadol's potential noninfringing uses show that their product is not adapted to infringing use, Plaintiffs' evidence that the *vast majority* of labelled uses would be infringing shows that the product *is* especially adapted to infringement (*i.e.*, polyneuropathic pain treatment). Moreover, contrary to Defendants' new position on appeal, Dr. Brown testified at trial that Defendants were seeking to sell the drug with the knowledge it would mostly be used to infringe and with instructions to use it in an infringing way. Appx9517-9518. Thus, Defendants' generic version of tapentadol, as labelled, is especially made or adapted to infringe.

CONCLUSION

The Court should reverse the district court's judgment that Actavis and West-Ward do not induce or contribute to infringement of 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 March 7, 2018.

/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 Circuit Rule 28.1(b)(3) because this brief contains 6,694 words, excluding parts of the brief exempted by Federal Circuit Rule 32(b) and Federal Rule of Appellate Procedure 32(f). 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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