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

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

GRUNENTHAL 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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RESPONSE BRIEF FOR CROSS-APPELLANT GRÜNENTHAL GMBH

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CERTIFICATE OF INTEREST

Counsel for Plaintiff-Cross-Appellant Grünenthal GmbH certify the following:

1. The full name of every party or amicus represented by me is:

   Grünenthal GmbH

2. The name of the real party in interest represented by me is:

   Grünenthal GmbH

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party represented by me are:

   Grünenthal Pharma GmbH & Co. KG

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:

   Finnegan, Henderson, Farabow, Garrett & Dunner, LLP: Joann Neth, Jennifer Roscetti, Marianne Terrot, Anthony Tridico, Kristi McIntyre, Megan Johns (fka Megan Leinen), Matthew Luneack

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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

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for Plaintiff-Cross-Appellant Grünenthal GmbH ("Grünenthal") state that no appeal in or from this same proceeding was previously before this Court or any other appellate court. Counsel are not aware of any other cases pending before this Court or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal.

COUNTERSTATEMENT OF JURISDICTION

Grünenthal agrees with the jurisdictional statements of West-Ward Pharmaceuticals International Limited, West-Ward Pharmaceuticals Corp. (collectively "West-Ward"), and Alkem Laboratories Limited ("Alkem") (collectively, with Actavis Elizabeth LLC, "Defendants"), but add that this Court has jurisdiction over Depomed, Inc.[1] and Grünenthal's (collectively "Plaintiffs") cross-appeal under 28 U.S.C. § 1295(a).[2]

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[1] Depomed has an exclusive license to the '364 patent at issue in this appeal. Appx35; Appx7769-7776 at Appx7770; Appx43960-44202 at Appx43965.

[2] Grünenthal notes that the district court entered judgment pursuant to Fed. R. Civ. P. 54(b) as there remains a pending and stayed claim for infringement of U.S. Patent No. 8,309,060.

INTRODUCTION

The claims of U.S. Patent No. 7,994,364 (the "'364 patent") are directed to a new crystalline form of tapentadol hydrochloride having particular characteristics. This new crystalline form ("Form A") is different from the previously known form (now called "Form B"), which was the original form of tapentadol hydrochloride synthesized by Dr. Helmut Buschmann in 1994.

Form A of tapentadol hydrochloride is more stable than Form B and can be advantageously used as an active ingredient in pharmaceutical compositions. Appx397 (1:55-68, 4:14-17). Form A was the product of a systematic investigation by four scientists at Grünenthal: Dr. Michael Gruss, Ms. Dagmar Lischke, Dr. Buschmann, and Dr. Andreas Fischer. Contrary to Alkem's suggestion that the invention of Form A was somehow trivial, Grünenthal spent almost a decade studying and characterizing the crystalline forms of tapentadol hydrochloride. Form A is the form used in Plaintiff Depomed's NUCYNTA® products, as well as all of Defendants' proposed generic products, for which Defendants stipulated to infringement.

In the district court, Defendants argued that the asserted claims of the '364 patent lack utility, and are anticipated, obvious, and unenforceable. The district court rejected all of these arguments, and issued an injunction ordering that the effective date of any approval of Defendants' generic products be no earlier than

the expiration date of the '364 patent (June 27, 2025). Appx25-27. On appeal, Alkem argues that the claims of the '364 patent are invalid as obvious, and West-Ward argues that the claims lack utility.

The district court correctly found that the asserted claims of the '364 patent were not obvious in view of Grünenthal's earlier patent on the chemical compound tapentadol itself and/or prior art discussing "polymorph screening," the general term for the process by which one investigates whether a particular compound is polymorphic and searches for possible polymorphs. In challenging the district court's obviousness conclusions, Alkem ignores the majority of the court's factual findings and the evidentiary record, which establish that polymorph screening involves complicated, unpredictable, trial-and-error experiments for which there was no reasonable expectation of success. Alkem also ignores, and in some cases outright rejects, relevant precedent from this Court and instead attempts to make its own law of obviousness to suit its needs.

As Alkem concedes, the district court "identified the proper legal standard" for obviousness. AlkemBr. 22. However, Alkem argues that the district court committed legal error by requiring "absolute predictability" to show obviousness (*id.* at 3, 5-6, 16, 22-23), and by creating an improper rule that polymorph patents can never be obvious (*id.* at 19-22). Alkem's arguments reflect a fundamental

misunderstanding of the district court's opinion and this Court's precedent upon which that opinion is based.

Likewise, the district court correctly concluded that the asserted claims of the '364 patent were not invalid for lack of utility. As the court explained, the '364 patent discloses two separate bases for utility: Form A of tapentadol hydrochloride is useful for treating pain, and is more stable than the previously known Form B. Indeed, there is no dispute that Form A is useful for treating pain or that it is more stable than Form B. Notwithstanding, West-Ward argues on appeal that the data disclosed in the '364 patent is insufficient to support this utility. West-Ward's arguments are contrary to the factual record, the district court's findings, and even Defendants' own experts. And the fundamental basis for West-Ward's argument, that the '364 patent discloses "nothing useful and new beyond the compound and treatment methods already claimed in the earlier '593 patent" (West-WardBr. 4), is refuted by black letter law from this Court that an invention need not be superior to the prior art to have sufficient utility under 35 U.S.C. § 101. *See Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1390 (Fed. Cir. 1988) ("The patent statute does not require that a patentable invention be superior to all prior devices."). The district court's opinion with respect to the '364 patent should be affirmed.

COUNTERSTATEMENT OF THE ISSUES

Whether the district court correctly held that Defendants failed to prove by clear and convincing evidence that claims 1-3 and 25 of the ’364 patent are invalid for obviousness and lack of utility.

COUNTERSTATEMENT OF THE CASE

I. Background on Tapentadol Hydrochloride

The ’364 patent claims a specific, new, crystalline form of the compound tapentadol hydrochloride. As the Principal and Response Brief for Cross-Appellant Depomed, Inc. explains, tapentadol hydrochloride was discovered by Grünenthal as part of an effort to find a “successor” for its opioid pain medication, tramadol. Appx8311-8312 (11:9-12:13); Appx46497-46528 at Appx46509; Appx46529-46622 at Appx46529. After ten years of unsuccessful searching, Grünenthal hired Dr. Buschmann to head up one of its laboratories. Appx8308-8312 (8:4-9:8, 10:7-11:8); Appx46497-46528 at Appx46504; Appx45910-45940 at Appx45917; Appx46040-46041.

Dr. Buschmann took Grünenthal in a completely different direction, jettisoning the fundamental teachings of tramadol. *See, e.g.*, Appx8319-8326 (19:23-26:3); Appx8328-8329 (28:20-29:5); Appx8380-8381 (80:11-81:6). On January 26, 1994, after synthesizing over 300 different compounds, Dr. Buschmann’s laboratory first synthesized tapentadol hydrochloride.

Appx45469-45902 at Appx45564; Appx8321-8322 (21:13-22:16); Appx8326-8327 (26:4-27:19); Appx44432-45082 at Appx44578. Positive animal results for tapentadol hydrochloride led to its selection as the lead drug candidate for larger-scale clinical trials, which ultimately supported its marketing approval. Appx8379 (79:11-24). To protect this new class of compounds, Grünenthal filed for patent protection and obtained U.S. Patent No. 6,248,737 (the "'737 patent").[3] Appx373-387; Appx439-464.

II. '364 Patent Background

A. Grünenthal Begins Analyzing Possible Polymorphism of Its Compounds

Polymorphism is the ability of a compound to crystallize in more than one crystal structure. Appx8528 (228:11-14). It occurs when there is more than one way of packing the molecules of a compound into a three-dimensional space, but importantly, it does not occur for all molecules. Appx9560 (30:8-17); Appx10778-10779 (202:17-203:1).

At the time of tapentadol's discovery by Dr. Buschmann in 1994, Grünenthal had not performed systematic polymorphism investigations on any of its compounds. Appx8326-8327 (26:10-27:5); Appx8530-8531 (230:13-231:6);

[3] 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. Appx439.

Appx8536 (236:18-22); Appx8378-8379 (78:14-79:10). In May 2000, Dr. Buschmann hired Grünenthal's first inorganic chemist, Dr. Michael Gruss, to establish a solid state facility at Grünenthal for investigating crystalline forms of Grünenthal's compounds. Appx8527-8528 (227:11-228:10); Appx8566 (266:11-19); Appx8378-8379 (78:14-79:10). Dr. Gruss was the first person to perform systematic polymorphism investigations at Grünenthal. Appx8530 (230:22-24). Because these studies require a lot of effort and resources, Dr. Gruss began investigating only a handful of Grünenthal compounds. Appx8531-8532 (231:19-232:1). One of these compounds was tapentadol hydrochloride. Appx8532 (232:2-10).

B. Grünenthal's Discovery of a New Crystalline Form of Tapentadol Hydrochloride

Prior to Dr. Gruss's arrival at Grünenthal, Dagmar Lischke, a lab technician in the Analytical Chemistry department, performed some early solid state studies on several Grünenthal compounds, including tapentadol hydrochloride. Appx8531 (231:7-15); Appx8533 (233:4-8). Based on her work at the time, Ms. Lischke suspected that there might be five or six crystal forms of tapentadol hydrochloride. Appx8533-8534 (233:24-234:3); Appx8539 (239:21-24). After his arrival, Dr. Gruss worked with Ms. Lischke to collect existing samples of tapentadol hydrochloride from various departments at Grünenthal, to produce new samples of

tapentadol hydrochloride, and to obtain new solid state analytical data on all of these samples. Appx8534 (234:4-12); Appx8554-8555 (254:18-255:10).

In 2001, Dr. Gruss reviewed X-ray Powder Diffraction ("XRPD")[4] and Differential Scanning Calorimetry ("DSC")[5] data on the tapentadol hydrochloride samples, and concluded that there were likely only two crystalline forms of the compound—a monoclinic crystal form (Form A) and an orthorhombic crystal form (Form B). Appx8534 (234:13-21); Appx8855-8856 (15:8-16:1); Appx59482-59514 at Appx59486, Appx59489. In making that assessment, Dr. Gruss compared the different XRPD patterns from different samples and grouped them together based on similar patterns. In the beginning, he did not know if certain XRPD patterns were patterns for a new form(s) of tapentadol hydrochloride or for samples that contained a mixture of different forms of tapentadol hydrochloride. Dr. Gruss analyzed the patterns and eventually determined that all the peaks in some patterns were also seen in the patterns for Form A or Form B, and thus the

[4] XRPD is used to obtain a fingerprint of the crystal structure of a given compound, also known as a diffraction pattern, by measuring the diffraction of X-rays applied to that sample. Appx8529 (229:7-12); Appx10498 (151:10-16). Each polymorph should have a unique XRPD pattern. Appx9561-9562 (31:14-32:6).

[5] DSC is a method where heat is applied to a sample and a reference, and the difference in the amount of heat that the samples take up is measured. DSC can be used to detect solid phase transitions such as melting or the transition from one polymorphic form to another. Appx8530 (230:6-12); Appx8541 (241:2-17); Appx9561 (31:2-13).

patterns he was reviewing were either Form A, Form B, or mixtures of Form A and Form B. Appx8546-8547 (246:3-247:5).

After determining that there were at least two forms of tapentadol hydrochloride, Dr. Gruss and the other inventors continued their characterization work and studies. In 2001, after studying pattern after pattern from various samples of tapentadol, Dr. Gruss discovered that the original tapentadol hydrochloride synthesized in Dr. Buschmann's lab in 1994—identified as Batch #0—consisted of only Form B. Appx8544 (244:9-22); Appx8555-8556 (255:24-256:12). To further investigate this finding, Grünenthal commissioned one of its employees, Marita Mueller, to synthesize tapentadol hydrochloride according to Example 25 of the '737 patent, which disclosed the synthesis of tapentadol hydrochloride. Appx8557 (257:3-24); Appx8558-8559 (258:24-259:20). Ms. Mueller's reproductions of Example 25 also proved to be Form B only. Appx8559-8560 (259:21-260:3); Appx8561 (261:11-19); Appx10497-10503 (150:20-156:15); Appx9729-9730 (7:17-8:18); Appx10525-10526 (178:11-179:10); Appx47929-47936; Appx47937-47939. Thus, Grünenthal determined that it had discovered Form A, a new crystalline form of tapentadol hydrochloride distinct from the form resulting from Example 25 of the '737 patent.

C. Grünenthal's Continued Work to Understand, Characterize, and Patent the New Form of Tapentadol Hydrochloride

At some point in 2001, Dr. Gruss and Dr. Buschmann decided to hire outside vendor SSCI to conduct an additional systematic polymorphism investigation on tapentadol hydrochloride. Appx8536-8537 (236:9-237:10); Appx8537 (237:18-22). Prior to hiring SSCI, the Grünenthal inventors had discovered Form A and distinguished it from Form B, and had characterized both forms as well. For example, Dr. Gruss explained that before the SSCI investigation, Grünenthal had "determined the lattice parameters of form B" and "had a single crystal structure investigation done on form A." Appx8537-8538 (237:19-238:3); *see also* Appx8854-8856 (14:21-16:1); Appx8859-8860 (19:7-20:18); Appx10923-10924 (46:10-47:16); Appx63392 (90:3-91:15); Appx49731-49771; Appx59482-59514 at Appx59486, Appx59489.

During this time, Grünenthal also discovered that Form A was the more stable polymorphic form at room temperature—although both forms can persist at room temperature. In DSC testing as well as in a variable temperature experiment that is disclosed in the '364 patent, it was shown that the point of transition or phase change from Form A to Form B occurs at a temperature between 40 and 50ºC. As both sides' experts explained at trial, a person of ordinary skill in the art of solid state chemistry would understand from this disclosure that at temperatures ***below*** 40ºC, Form A is the more thermodynamically stable form. Appx10471-

10472 (124:9-125:6); Appx9694-9696 (57:24-59:7). This was noteworthy given the fact that Form B of tapentadol hydrochloride, the form originally made by Dr. Buschmann in 1994 as "Batch #0," remained only Form B when it was tested almost eight years later. Appx8543-8544 (243:19-244:22); Appx8555-8556 (255:24-256:12); Appx9730-9731 (8:23-9:16); Appx10820-10823 (244:14-247:1).

At trial, Dr. Gruss testified that there was continuous work at Grünenthal on the tapentadol hydrochloride polymorphism investigation until he left the company in 2014, noting that "as time went by, the more and more experiments we did, the more information we gathered." Appx8534 (234:4-8); Appx8535 (235:13-23). As Dr. Gruss explained, a polymorphism screen or investigation is never finished: it is possible that "after a hundred years, you might experience a new form." Appx8535 (235:20-23).

Ultimately, Dr. Gruss and the other inventors filed a patent application to protect their newly discovered form of tapentadol hydrochloride. In the '364 patent, Grünenthal claimed, *inter alia*, crystalline "Form A" of tapentadol hydrochloride. As set forth above, Form A of tapentadol hydrochloride was the product of a systematic and targeted investigation conducted by scientists at Grünenthal to characterize the crystalline landscape of tapentadol hydrochloride, an effort that spanned a decade. When tapentadol hydrochloride was first synthesized, only what is now called Form B of tapentadol hydrochloride existed.

Appx8543-8544 (243:19-244:22); Appx8555-8556 (255:24-256:12); Appx10519-10522 (172:19-175:6); Appx132-133; Appx135; Appx137; Appx63900 (38:19-24); Appx10497-10500 (150:20-153:6); Appx10802-10804 (226:20-228:16). Alkem's suggestion that Form A existed from the beginning, or alternatively that it was the product of a "routine," "easy and fast" "polymorph screen" conducted by third-party contractor SSCI (AlkemBr. 4-5, 12-13) is completely contrary to the undisputed evidence at trial.

D. The Asserted Claims of the '364 Patent

As Grünenthal explained in the specification of the '364 patent, "[i]t has now been surprisingly found that [tapentadol hydrochloride] can be produced in a reproducible manner in two different crystal forms," and that "[t]he present invention provides a new form (Form A) of [tapentadol hydrochloride] which is different from the form already known (Form B) . . . ." Appx397 (1:55-63). Plaintiffs asserted claims 1-3 and 25 of the '364 patent against Defendants. Claim 1 recites a "crystalline Form A" of tapentadol hydrochloride having an XRPD pattern exhibiting peaks at certain 2-theta values (the x-axis on an XRPD pattern). Appx405-406. Claim 2 depends from claim 1 and recites the "crystalline Form A" of claim 1 exhibiting certain additional XRPD peaks. Appx406. Claim 3 recites the "crystalline Form A" of claim 1 exhibiting an XRPD pattern that is "essentially the same as" that provided in Figure 1 of the '364 patent. *Id.* Claim 25 recites a

"solid pharmaceutical composition, comprising, as an active ingredient, a crystalline Form A" of tapentadol hydrochloride having certain XRPD peaks "and at least one suitable additive or auxiliary substance." *Id.*

Samples of the generic products from each Defendant were analyzed and found to consist almost entirely of Form A. Defendants did not attempt to dispute that finding, nor did they attempt to redesign their products to not infringe. Instead, Defendants each stipulated to infringement of the '364 patent. Appx38.

III. To Support Its Invalidity Arguments, Alkem Mischaracterizes the Factual Record

A. Alkem Mischaracterizes the Underlying Facts and the Work that Grünenthal Did to Discover and Characterize the New Form of Tapentadol Hydrochloride

On appeal, Alkem asserts that Form A of tapentadol hydrochloride has always existed at Grünenthal—it has not—that Form A is easy to obtain—it was not—and that Form A invariably results whenever you make tapentadol hydrochloride—it does not. None of these pronouncements are supported by the facts and evidence presented in this case.

Alkem's assertion in its brief that SSCI "simply did what was already published in the Byrn article . . . to conduct [its] polymorph screen" (AlkemBr. 13) is incorrect. A polymorph screen involves applying various parameters and combinations thereof to the crystallization of a compound, such as various solvents and conditions, to understand and characterize the crystalline landscape of the

compound under investigation. Appx8528 (228:15-21); Appx10485-10486 (138:13-139:2); Appx10493 (146:11-19); Appx10494 (147:20-25). Grünenthal provided input to SSCI on the solvents and other conditions to be used for the polymorph screen based on the manufacturing process and other data Grünenthal already had developed for tapentadol hydrochloride. Appx59447-59462 at Appx59457-59458. This included a number of solvents that were not listed in the 1995 article by Stephen Byrn ("Byrn") (Appx57372-57381) upon which Alkem relies. Appx49380-49567 at Appx49393-49394 (1-butanol, DCM, DMF, MEK, THF, and toluene); Appx57372-57381 at Appx57373.

Alkem relies on SSCI's experiments, many of which yielded Form A, to argue that "[a] person of ordinary skill in the art would not have done anything differently than what Grünenthal and SSCI did . . . and would have seen Form A present." AlkemBr. 13. But Alkem misses the crucial point that the starting material SSCI used for its polymorph screen was ***determined upon arrival to be Form A***. Appx49380-49567 at Appx49388, Appx49392; Appx10906 (29:6-8). Given that many of the experiments that resulted in Form A are "slurry" experiments in which crystals are not fully dissolved (Appx49380-49567 at Appx49393-49394) and therefore maintain their crystalline structure, it is not at all surprising that the experiments yielded at least some of the more stable Form A. Likewise, Alkem relies on the "inherent properties" of tapentadol hydrochloride

(such as the fact that Form A is more stable than Form B) to argue that "***any*** person of ordinary skill in the art would have happened across Form A; it would have taken luck or extreme and improbable conditions to obtain only Form B, without any trace of Form A." AlkemBr. 14. These arguments ignore the fact that when tapentadol hydrochloride was first made at Grünenthal, ***only Form B of tapentadol hydrochloride existed***. Appx8543-8544 (243:19-244:22); Appx8555-8556 (255:24-256:12); Appx10519-10522 (172:19-175:6); Appx132-133; Appx135; Appx137; Appx63900 (38:19-24); Appx10497-10500 (150:20-153:6); Appx10802-10804 (226:20-228:16). It is undisputed that Form B is metastable at room temperature and that it can persist at room temperature for years, even though it is not the most thermodynamically stable form at that temperature. Appx10818-10819 (242:2-243:22); Appx9829-9830 (107:20-108:4); Appx9831-9832 (109:24-110:3); Appx9614-9616 (84:3-86:2); Appx9730 (8:19-22); Appx9730-9731 (8:23-9:16); Appx10820-10823 (244:14-247:1).

B. Alkem Misleads the Court by Mischaracterizing the Form of Tapentadol Hydrochloride Disclosed in the '737 Patent

Alkem's characterization of the prior art '737 patent vacillates between misleading and demonstrably false. In the district court, Alkem argued that the '364 patent is anticipated by the '737 patent, which discloses, among other compounds, the synthesis of tapentadol hydrochloride as Example 25. The district court rejected this argument, and Alkem does not appeal that aspect of the court's

decision. Nonetheless, Alkem continues to argue on appeal that the University of Wisconsin scientists it hired "tested the prior art synthesis disclosed in Example 25 of the '737 patent—the results of which revealed mixtures of Form A and Form B—to show that the prior art inherently anticipated" Form A. AlkemBr. 9. Alkem's reliance on these "results" is contrary to the express findings of the district court that the "record reflect[ed] only ***one synthesis*** by the University of Wisconsin scientists, which consisted of ***less than all of the steps enumerated in the ['737] patent***." Appx132 (emphases added). All of the other evidence in the record, which Alkem does not challenge on appeal, firmly establishes that the faithful reproduction of Example 25 yields only Form B. Appx8559-8562 (259:17-262:22); Appx9729-9730 (7:17-8:18); Appx10497-10506 (150:20-159:4); Appx10525-10526 (178:11-179:10); Appx64016 (154:2-7); Appx47929-47936; Appx47937-47939. The finding of no anticipation was not appealed, so it is the law of the case.

Incredibly, Alkem goes so far as to assert that "it was undisputed that even just practicing the protocol in the '737 patent—without any further polymorph screen—resulted in either Form A or Form B tapentadol hydrochloride." AlkemBr. 10; *see also id.* at 34. That proposition is, in fact, ***vigorously disputed***: Plaintiffs-Cross-Appellants' position is and always has been that faithfully reproducing the protocol of the '737 patent (unlike Defendants' single truncated

reproduction of just one of three steps of Example 25) yields ***only Form B***. Appx131-135; Appx137. The district court found that Defendants had not met their burden of proving the contrary proposition. Appx137.

Alkem's assertion that "Grünenthal even admitted at trial that the compounds 'obtained by the procedure described in example 25 of U.S. Pat. No. 6,248,737' were in fact Form A tapentadol" (AlkemBr. 34) is demonstrably false. The evidence Alkem cites establishes only that the material Grünenthal sent to third-party contractor SSCI was tested upon arrival and determined to be Form A. *See id.* (citing Appx49384; Appx49392; Appx63720 (50:18-52:7); Appx63721 (57:14-58:9, 58:19-59:3, 59:9-10, 59:12-18); Appx63395 (102:5-10); Appx6339 (107:12-16); Appx10906 (29:6-8)). Alkem apparently suggests that this material was made according to Example 25 of the '737 patent, but points to no manufacturing evidence on how the sample sent to SSCI was made or the conditions under which the sample had been exposed prior to SSCI's testing. The fact that Grünenthal sent SSCI a sample of tapentadol hydrochloride that upon arrival consisted of Form A in no way suggests that Grünenthal admitted that material made according to Example 25 was Form A.[6] To the contrary, the only

[6] Alkem's allegations regarding purported "misrepresentations" in Grünenthal's patent application are also wrong (Appx152) and irrelevant to the obviousness determination, the only issue which Alkem has appealed.

evidence in the record on this issue is that the only form of tapentadol hydrochloride made by Example 25 is Form B—the same form made by Dr. Buschmann's original synthesis (Batch #0) as shown by the XRPD analysis Grünenthal performed on Batch #0 over 7 years after synthesis. The district court properly rejected Alkem's argument. Appx136.

Finally, just like its other misstatements, Alkem's argument that the '737 patent "disclosed crystalline tapentadol hydrochloride" (AlkemBr. 8-10) is also incorrect. The district court found that "[w]hile Example 25 [of the '737 patent] states that tapentadol hydrochloride 'crystallized out' at the end of the synthesis . . . , the patent ***does not*** discuss the solid state crystal form of tapentadol hydrochloride." Appx63 (emphasis added). As the court explained, "[t]he crystal form landscape for a particular compound can include polymorphs, solvates, hydrates, and polymorphs of solvates and hydrates" (Appx139), and the '737 patent is silent as to whether the solid that "crystallised out" of solution may or may not have been a polymorph, solvate, hydrate, or a mixture of materials. In fact, Dr. Buschmann testified that "crystallised out" was a reference to "the powder which was solidified coming out of solution [which] was considered as the crystalline powder." Appx8461 (161:13-18); *see also* Appx8460-8461 (160:24-161:3). The '737 patent simply contains no information on the form of tapentadol hydrochloride produced by Example 25.

IV. Trial

Plaintiffs asserted claims 1-3 and 25 of the '364 patent against Defendants. Before trial, all Defendants stipulated to infringement of the '364 patent, but continued to argue that it was invalid and unenforceable under the doctrine of unclean hands. Appx38-39. The district court then held a bench trial and received post-trial briefing from the parties. Of relevance to this appeal, the court held that Defendants would infringe claims 1-3 and 25 of the '364 patent, which are neither invalid nor unenforceable. Appx25-27.

A. Validity

1. The '364 Patent Claims Are Not Anticipated[7]

The district court rejected Defendants' argument that the asserted claims are invalid as inherently anticipated by Example 25 of the '737 patent. Appx128-137. Specifically, the district court found that Defendants failed to meet their burden of proving by clear and convincing evidence that the practice of the complete procedure set forth in Example 25 "necessarily and inevitably" results in the production of polymorphic Form A. Appx128-129 (quoting *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003)).

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[7] Although Alkem is not seeking review of the district court's decision on anticipation, Alkem nonetheless reiterates its anticipation arguments in support of its obviousness position on appeal. These arguments, which are belied by the evidentiary record, fare no better in the context of obviousness.

In support of their inherent anticipation contention, Defendants had commissioned scientists at the University of Wisconsin to perform a synthesis that Defendants contended is consistent with the procedure of Example 25. Appx130-132. However, as Defendants' expert, Dr. Steed, admitted (as he had to), the University of Wisconsin scientists only performed the last of the three steps of Example 25. Appx131. The district court found that this "one synthesis . . . consisted of less than all of the steps enumerated in the patent and produced a mixture of Form A and Form B crystals." Appx132. The court also found that the syntheses of Example 25 performed by Grünenthal employee Marita Mueller, in which Ms. Mueller "performed all of the steps of Example 25 and produced Form B, weigh against a determination that Defendants have proven inherent anticipation by clear and convincing evidence." Appx135-136. In view of this evidence, the district court held that the '737 patent does not anticipate crystalline Form A of tapentadol hydrochloride. Appx137. Defendants do not contest this finding on appeal.

2. The '364 Patent Claims Are Not Obvious

The district court also rejected Defendants' argument that the asserted claims of the '364 patent are invalid for obviousness in view of the '737 patent in combination with knowledge in the field about polymorph screening. As a preliminary matter, the district court found that "[t]here is nothing in particular in

the ’737 patent that would have motivated a POSA studying crystal structure to select tapentadol hydrochloride from amongst the many compounds disclosed in the ’737 patent.” Appx142. With respect to Defendants’ argument that polymorph screening is routine, the court found that Plaintiffs demonstrated that “polymorph screening consists of an unpredictable application of those routine techniques,” and that “the results of the polymorph screen . . . would have been impossible to predict.” Appx143-144; *see also* Appx144 (noting that “predictability is a touchstone of obviousness” (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009))). The court also explained that in a number of recent polymorph patent cases, the defendants, like Alkem herein, “contended that a POSA would have been motivated to discover [a] claimed polymorph, and in each case the court ***rejected*** this argument.” Appx144-145 (emphasis added) (citing cases).

3. The ’364 Patent Claims Meet the Utility Requirement

Finally, the district court rejected Defendants’ argument that the claims of the ’364 patent are invalid for failure to meet the utility requirement of 35 U.S.C. § 101. The court found that the ’364 patent explicitly references the ’737 patent, which teaches that tapentadol hydrochloride is useful for treating pain, that in 2004 it was generally known in the art that tapentadol hydrochloride was useful as an analgesic, and indeed that “there is no dispute that Form A of

tapentadol hydrochloride is useful as an analgesic." Appx146. "In addition to being useful as an analgesic," the court explained that the '364 patent states that Form A is "more stable under ambient conditions," and "can be advantageously used as [an] active ingredient in pharmaceutical compositions," disagreeing with Defendants that this statement is ambiguous. Appx146-147 (quoting '364 patent at 4:13-17 [Appx398]). The court also rejected Defendants' argument that there is nothing in the '364 patent to suggest that the more stable form of tapentadol hydrochloride is the more useful form for pharmaceutical activity, stating that Defendants' argument appears to import a nonexistent requirement into the patent statute that the claimed invention be "better" than the prior art. Appx147-148 (citing *Demaco Corp.*, 851 F.2d at 1390). Finally, the court found that Example 16 of the '364 patent provides empirical evidence to support the statement in the '364 patent that Form A is more stable, and that Defendants' expert, Dr. Steed, agreed that this was the case. Appx148.

STATEMENT OF JOINDER

Grünenthal joins, expressly adopts, and incorporates by reference Cross-Appellant Depomed, Inc.'s Principal and Response Brief in its entirety. *See* Fed. R. App. P. 28(i).

SUMMARY OF ARGUMENT

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 '364 patent are invalid.

First, the district court correctly found that the asserted claims of the '364 patent were not obvious in view of Byrn and U.S. Food and Drug Administration ("FDA") guidance on polymorph screening. The record showed that polymorphism generally and Form A of tapentadol hydrochloride specifically are completely unpredictable, which is a touchstone of the obviousness analysis. Moreover, it showed that polymorph screening involves complicated, unpredictable, trial-and-error experiments for which there was no reasonable expectation of success. Established precedent holds that the results of such experiments were not obvious or obvious to try.

Second, the district court correctly found that the asserted claims of the '364 patent are not invalid for lack of utility. The court found that the '364 patent discloses two separate bases for utility. First, it discloses that Form A of tapentadol hydrochloride is "useful for treating pain." Second, it discloses that Form A of tapentadol hydrochloride is more stable than Form B and is thus useful for pharmaceutical compositions. The court found that both these bases of utility are supported by the '364 patent. Appx146.

STANDARD OF REVIEW

"Obviousness is a question of law based on underlying questions of fact." *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (citing *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1348 (Fed. Cir. 2000)). Thus, the Federal Circuit "review[s] the ultimate determination of obviousness by a district court *de novo* and the underlying factual inquiries for clear error." *Id.*

"Whether an invention claimed in a patent lacks utility is a question of fact, which [the Federal Circuit] therefore review[s] for clear error." *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180 (Fed. Cir. 1991) (citing *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984)). "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." *Impax Labs., Inc. v. Aventis Pharm., Inc.*, 468 F.3d 1366, 1375 (Fed. Cir. 2006) (quoting *Hoffmann–La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1359 (Fed. Cir. 2003)).

ARGUMENT

"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, 102 (2011) (citation 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) (citations omitted).

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 '364 patent are invalid. The court's judgment as to those issues, set forth in a detailed 167-page opinion, should be affirmed.

I. The District Court Correctly Held that the Asserted Claims of the '364 Patent Are Not Invalid for Obviousness

The district court correctly found that the asserted claims of the '364 patent were not obvious in view of Byrn (Appx57372-57381) and FDA guidance on polymorph screening (Appx57278-57324). Appx137-145. In challenging the district court's obviousness conclusions, Alkem ignores the majority of the court's factual findings and the evidentiary record, as well as the relevant precedent on which the court's opinion is based.

A. The Byrn Reference Does Not Render the Claims Obvious

1. The District Court Correctly Concluded that Byrn Does Not Render the Claims of the '364 Patent Obvious

As it did before the district court, Alkem argues on appeal that the '364 patent claims are obvious in view of "published prior art crystallization techniques" in the Byrn reference. AlkemBr. 27-36. The district court considered Alkem's arguments and expert testimony with respect to the Byrn article, but found while there may be known techniques "used to explore the polymorph landscape," these techniques "include[] a large variety of conditions that could be appropriate for a particular polymorph screen, including solvent, temperature, stirring, cooling rate, seeding, and whether an anti-solvent is used." Appx143. The court further found that "the variability of these conditions produces a huge number of possible choices that must be made during the course of a polymorph screen." *Id.*

This Court has explained that in such situations, where researchers can only "vary all parameters or try each of numerous possible choices until one possibly arrives at a successful result, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful," "courts should not succumb to hindsight claims of obviousness." *See Procter & Gamble v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 996-97 (Fed. Cir. 2009) (alterations in original) (citations omitted); *see also Merck*

& Co. v. Sandoz, Inc., Nos. 10-1625, 10-2308, 2012 WL 266412, at *2, *4 (D.N.J. Jan. 30, 2012) (the proper question is not whether the invention "is the result of routine pharmaceutical development," but whether a "skilled artisan, at the beginning of the development process, would have viewed the final outcome of the process as one of a finite number of identified, predictable solutions").

The district court also relied on the unpredictability of both the claimed invention itself and the experiments required to produce it, stating that "while each individual technique performed during a polymorph screen may be routine, polymorph screening consists of an unpredictable application of those routine techniques," and further that "the results of the polymorph screen . . . would have been impossible to predict." Appx143-144. The district court did not err in concluding that such unpredictability supported the conclusion of nonobviousness under established precedent. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("the fact that a combination was obvious to try might show that it was obvious" only if "there are a finite number of identified, predictable solutions" that lead to anticipation of success); *DePuy Spine*, 567 F.3d at 1326 ("predictability is a touchstone of obviousness"); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on . . . 'identified, predictable solutions' may present a difficult hurdle [for patent challengers] because potential solutions are less likely to

be genuinely predictable."); *see also In re Armodafinil Patent Litig. Inc.*, 939 F. Supp. 2d 456, 502 (D. Del. 2013) ("Thus, even if the general idea of using crystallization experiments were obvious to try, such unpredictable trial and error experimentation fails to render [the crystal form] obvious because the testing required was more than simply routine.").

Relying solely on the Byrn article, Alkem boldly asserts that "so long as the technique to perform the polymorph screen was known and routine and employed with a reasonable expectation of success, the resulting polymorphs are obvious . . . ." AlkemBr. 29. The Supreme Court has explicitly rejected such "rigid and mandatory formula[e]." *KSR*, 550 U.S. at 419. At any rate, Alkem did not establish that there was a reasonable expectation of success, for example, by establishing that there is some standard, one-size-fits-all polymorph screen through which a person of ordinary skill would reasonably expect to succeed for tapentadol hydrochloride. Appx10794 (218:11-19). Instead, Alkem simply concludes in hindsight that there would have been a reasonable expectation of success, ignoring the district court's clear factual findings (Appx139-144), and this Court's precedent under which there could be no reasonable expectation of success in arriving at the invention claimed in the '364 patent. *See*, *e.g.*, *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 555 F. App'x 961, 971 (Fed. Cir. 2014) (process being "complicated, unpredictable and largely conducted through trial and error . . .

would have precluded argument by Appellants that there would have been a reasonable expectation of success"); *see also Merck & Cie v. Watson Labs., Inc.*, 125 F. Supp. 3d 503, 514 (D. Del. 2015) ("While there may have been a motivation to discover new crystalline polymorphs of MTHF, doing so would have required a process of trial and error. There was therefore no reasonable expectation of success of finding Type I crystals."), *rev'd on other grounds [on-sale bar]*, 822 F.3d 1347 (Fed. Cir. 2016).

Alkem attempts to distinguish the many district court cases that refute its position by arguing that, in those cases, the "parties challenged polymorph patents by referring generally to the knowledge of a person of ordinary skill, without referencing Byrn, indeed any particular prior art that provided the details for a polymorph screen." AlkemBr. 36. Even a cursory review of these cases and the underlying briefing reveals that Alkem has completely mischaracterized them. For example, in *In re Armodafinil*, the court found that "defendants' contention based on allegedly 'obvious to try' ***experiments*** to prepare the most stable form of armodafinil falls short of proving that Form I would have been obvious." 939 F. Supp. 2d at 501 (emphasis added). The court explained that the defendants' obviousness argument was based on "***references*** [that] were presented at trial to provide greater detail as to the ***state of the art*** in the early 2000s." *Id.* at 489 n.43 (emphases added); *see also id.* at 490 n.45 ("Specifically, the defendants

referenced: Bryn [sic], S. et al, *Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*, Pharm. Res. 12(7):945-954 (1995) . . . ."). Alkem is incorrect that the defendants in those cases challenged the polymorph patents at issue only by "referring generally to the knowledge of a person of ordinary skill." AlkemBr. 36. To the contrary, the defendants in those cases asserted a multitude of references just like the Defendants herein.

Likewise, Alkem claims that in *Merck*, the parties' experts "did not discuss or address known prior art techniques." *Id.* at 37 (citing 125 F. Supp. 3d at 514). To the contrary, the defendants' expert's obviousness argument was based entirely on a known prior art technique, specifically, a patent that "disclose[d] a detailed synthetic and recrystallization method for obtaining a specific end product." Defendant's Corrected Opening Post-Trial Brief, *Merck & CIE v. Watson Labs, Inc.*, Nos. 13-978-RGA, 13-1272-RGA, 2015 WL 13119308, at *18 (D. Del. July 21, 2015).

2. Alkem's Arguments with Respect to Byrn Are Classic, Prohibited Hindsight

In its brief, Alkem spills considerable ink arguing that SSCI, an outside vendor to whom Grünenthal sent samples of tapentadol hydrochloride (subsequently determined to be Form A), ran a polymorph screen on those samples

using some of the solvents listed in the Byrn article and frequently found Form A.[8] AlkemBr. 4-5, 12-14. Alkem argues that "[t]he fact that a person of ordinary skill in the art would have seen Form A present when doing a prior art polymorph screen" (which is neither true nor the standard for obviousness) "is confirmed by the nature of tapentadol hydrochloride itself" because tapentadol hydrochloride "has only two polymorphs that have been discovered to date: Form A and Form B." *Id.* at 13-14; *see also id.* at 5 ("Byrn's lab found that there were only two readily-available polymorphs for tapentadol."). Alkem further asserts that "Form A is the one which is ordinarily stable at room temperature," and thus that it would be the form a person of ordinary skill in the art would find upon performing the polymorph screen set forth in Byrn. *Id.* at 14. Alkem's entire argument is built on a hindsight analysis.

Alkem completely ignores the fact that ***none of the foregoing was known or knowable*** at the time of the '364 patent. Indeed, as the trial record showed, as the district court found, and as Alkem appears to admit on appeal (*id.* at 8, 27), this would have been completely unpredictable at the outset. For example, as even Defendants' expert conceded, a person of ordinary skill would not have known how many polymorphs, if any, existed, or which were the most stable. Appx8567

[8] As discussed *supra* Counterstatement of the Case Section II.C, SSCI's polymorph screen started with Form A. SSCI did not discover or invent Form A.

(267:13-21); Appx9772-9773 (50:11-51:10); Appx9767-9770 (45:7-48:9); Appx10773-10777 (197:15-201:19); Appx10782 (206:1-7). Thus, while Alkem can now look back and observe that when SSCI performed a polymorph screen, it found Form A in many instances (AlkemBr. 12-13), a person of ordinary skill could not have predicted that he or she would have found Form A, or any other crystal form, given that it was not known whether tapentadol hydrochloride would have ***any*** polymorphic forms at all, much less any particular crystalline form. And it is now known that Example 25 of the '737 patent produces only ***Form B***. *See supra* Counterstatement of the Case Section II.B.

It is not, and has never been, Plaintiffs' position (or the district court's position) that in order to be obvious, one must have the ability to "absolutely" predict the number of polymorphic forms that tapentadol hydrochloride would have or their respective stabilities. Instead, Plaintiffs' argument is that Alkem cannot simply rely on the fact that ***Grünenthal*** discovered that there were two crystalline forms of tapentadol hydrochloride, and that ***Grünenthal*** discovered that Form A is more stable than Form B, to support its argument that Form A would have been obvious at the time of the invention before all that was known. That is the epitome of hindsight, and it is per se improper. *Para-Ordnance Mfg. v. SGS Imps. Int'l, Inc.*, 73 F.3d 1085, 1087 (Fed. Cir. 1995) ("Obviousness may not be established using hindsight or in view of the teachings or suggestions of the

inventor."); *see also In re Armodafinil*, 939 F. Supp. 2d at 502 (defendants' argument that a crystal form would have been obvious was "based on an impermissible hindsight analysis, because a person of ordinary skill in the art in 2002 would not have known of the existence of Form I, and could not have known the method to produce Form I with any solvent").

Alkem also argues, in hindsight, that because Form A was allegedly "easy" to discover, Form A must have been obvious at the time of its invention. *See, e.g.*, AlkemBr. 13 ("There is no dispute that this was an easy and fast procedure for third-party SSCI to conduct."); *id.* at 21 (stating that polymorphs that are "difficult to obtain" may not be obvious); *id.* at 33 ("In **just three weeks**, SSCI reported back to Grünenthal with its first results—those easiest to obtain—reflecting the standard conditions from the Byrn article."). This line of argument also relies on hindsight, as of course, a person of ordinary skill would not have known at the outset whether or not it would be difficult to find Form A or any polymorphic form of tapentadol hydrochloride. *Procter & Gamble*, 566 F.3d at 996-97. Furthermore, a person of ordinary skill would not have known whether to stop looking when he or she found Form A, or whether there would be other forms that are more stable than Form A. Appx8805 (235:13-23); Appx10782-10783 (206:8-207:5). At any rate, Alkem's argument suggesting that a product is obvious because it was "easy" to find, or because it was discovered relatively quickly is

contrary to the patent statute, which states that "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103(a) (pre-AIA).

3. The District Court Did Not "Erroneously Discount" the Byrn Article

Alkem argues that the district court "erroneously discounted the Byrn article by relying on other district court cases that never addressed [it]." AlkemBr. 36-38. This argument is meritless for several reasons. As a preliminary matter, there is no evidence that the district court "discounted" the Byrn article at all. To the contrary, the court discussed in detail the exact portions of the Byrn article that Defendants rely on here, and recounted Defendants' various arguments with respect to the article below. Appx138; Appx141-143; Appx145. That the court noted that Byrn was "published in 1995, long before many of the cases discussed above" (Appx145), does not mean that the court did not consider the article.

Perhaps recognizing that the case law on polymorph patents is decidedly not in its favor, Alkem attempts to paint Byrn as the "missing piece" of prior art under which prior cases would have been decided differently. *See, e.g.*, AlkemBr. 37 ("Here, unlike in prior cases, Byrn provided express guidance about how to screen polymorphs."); *id.* at 38 (stating that there is an "obvious difference" between "this case—which relied upon the Byrn article's explicit guidance on routine methods for screening polymorphs—and prior cases—which did not"). But the reality is

that Byrn is substantially similar to several other pieces of prior art that the district court in this case (as well as others) considered as part of its conclusion that the polymorph patent at issue was valid and nonobvious. Once again, Alkem ignores that the district court explained that "it is undisputed in this case that methods for conducting polymorph screening were known in the art." Appx145. Thus, the district court expressly considered the known "methods for conducting polymorph screening" from Byrn upon which Alkem relies on so heavily, and nonetheless found the claims at issue to be nonobvious in light of those known methods. Accordingly, there is no basis to disturb the district court's finding because the Byrn reference may not itself have been specifically mentioned in some of the district court decisions relied upon.

Alkem is also flat wrong that "[t]here was no indication that the Byrn article ***was even of record*** in any of the prior district court decisions" that the district court relied upon. AlkemBr. 38. For example, Byrn was expressly considered in *In re Armodafinil*, one of the primary cases the district court relied upon. *See* 939 F. Supp. 2d at 490 n.45. Indeed, at closing arguments, Defendants made the same argument—that "the District Court cases that Plaintiffs rely upon did not have the Byrn reference." Appx64182-64183 (156:20-157:4). In response, Plaintiffs pointed out that the Byrn article was considered in the *In re Armodafinil* case, even

pointing the district court to the specific part of the opinion where Byrn was cited. Appx64212 (186:1-12). Alkem chooses to utterly ignore this exchange.

B. The FDA Guidance Does Not Render the Claims Obvious

Alkem's argument that "in 1987 the FDA guided pharmaceutical companies to conduct screens for polymorphs" (AlkemBr. 4; *see also id.* at 10-12) also does not render the claims at issue in the case at bar obvious. As a preliminary matter, Alkem's characterization of this FDA guidance as a "requirement" for polymorph screening (*id.* at 33, 40) is misleading. As Alkem acknowledges elsewhere in its brief, the FDA document merely sets forth "***guidance***" or "***guidelines"*** (*id.* at 7, 11) that "[a]ppropriate analytical procedures ***should*** be used to determine whether (or not) polymorphism occurs." Appx57278-57324 at Appx57314 (emphasis added).

The district court in this case specifically discussed the fact that "[a]s early as 1987, the FDA had issued guidelines" regarding polymorphism, and went on to find that a "POSA would have understood as of June 2004 how to conduct a polymorph screen and that there were publications that provided guidance how to do such a screen," for example, the Byrn reference. Appx139-140. The district court went on to explain that in a number of recent polymorph patent cases, the defendants argued—like Alkem does here—"that a POSA would have been motivated to discover [a] claimed polymorph, and in each case the court ***rejected***

this argument." Appx144-145 (emphasis added) (citing cases). Indeed, as with the Byrn reference, the court in *In re Armodafinil* specifically considered the ***same 1987 FDA guidelines*** Alkem relies on here, and nonetheless found claims to a crystal form of armodafinil nonobvious. 939 F. Supp. 2d at 500 (noting that "for a patent challenger to establish obviousness, it is insufficient to allege a general motivation to discover an undefined solution that could take many possible forms" (citing *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373-74 (Fed. Cir. 2008))).

Likewise, in *Merck*, the court found claims to a crystal form of MTHF nonobvious notwithstanding the finding that "[t]here was motivation in the industry to find and characterize new crystalline polymorphs of MTHF." 125 F. Supp. 3d at 514; *see also Takeda Pharm. Co. v. Handa Pharm., LLC*, No. C-11-00840 JCS, 2013 WL 9853725, at *30, *74 (N.D. Cal. Oct. 17, 2013) (finding claims to crystal form of dexlansoprazole nonobvious notwithstanding its findings that "a person of ordinary skill in the art would have been motivated to select dexlansoprazole for use as a pharmaceutical" and would have "been motivated to crystallize it").

Moreover, the district court specifically found that "[t]here is nothing in particular in the '737 patent that would have motivated a POSA studying crystal structure to select tapentadol hydrochloride from amongst the many compounds

disclosed in the '737 patent" for a polymorph screen based on the FDA guidance. Appx142. Alkem characterizes that finding as "unsupported." AlkemBr. 31. But the district court relied on the testimony of Defendants' own expert, Dr. Steed, for this point. Appx142 (citing 3/16/2016 Tr. (Steed) [Appx9772] at 50:5-10). The record shows that polymorph screens involve a great deal of effort and resources. Appx8531-8532 (231:19-232:1). Indeed, Grünenthal spent years investigating the polymorphism of just one compound: tapentadol hydrochloride. Appx8534 (234:4-8); Appx8535 (235:13-23). Thus, even though "the '737 patent itself discloses only 28 example compounds" (AlkemBr. 32) from the substantial genus disclosed and claimed, a person of ordinary skill would have no reason to perform a polymorph screen on all of these twenty-eight compounds based on the FDA guidance. And a person of ordinary skill would have "no reason to select tapentadol hydrochloride" as Alkem claims (*id.*) from amongst the twenty-eight examples of the '737 patent, let alone the vast numbers of compounds that had been patented or disclosed to have therapeutic potential around the time of the '364 invention.[9]

[9] Alkem also points to a 2002 World Health Organization's listing of International Nonproprietary Names for Pharmaceutical Substances that includes tapentadol as somehow providing a "reason to select tapentadol hydrochloride" "because tapentadol hydrochloride was specifically identified as a useful analgesic in the prior art." *Id.* at 32-33. Yet, that reference provides the same information as the

The district court also did not require Alkem to prove a "lead compound" analysis as Alkem contends the court "implied." AlkemBr. 31. The court's opinion nowhere mentions a "lead compound" analysis with respect to the '364 patent, and does not cite any "lead compound" authority (as it did, for example, in its analysis of the '593 patent, Appx96-97). Even if the district court had required the Defendants to undertake a lead compound analysis, it would not be improper to do so, and indeed may be required, given that a polymorph is a "new" compound with "new" and distinct characteristics. *Incyte Corp. v. Concert Pharm. Inc.*, IPR2017-01256, 2017 WL 4764828, at *5-6 (PTAB Oct. 19, 2017) (applying lead compound analysis to a deuterated compound) (citing *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-93 (Fed. Cir. 2012); *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

Instead, the court simply noted in one sentence that "[t]here is nothing in particular in the '737 patent that would have motivated a POSA studying crystal structure to select tapentadol hydrochloride from amongst the many compounds disclosed in the '737 patent." Appx142. Motivation is a common part of the

'737 patent itself did—it identifies the chemical name and structure of tapentadol and states that it is an "analgesic"; Alkem identifies no further testimony explaining any purported significance of the reference. Appx580570-58147 at Appx58128. This reference standing alone provides no reason to conduct a polymorphism investigation on tapentadol hydrochloride.

standard obviousness analysis. Indeed, Alkem's brief mentions it repeatedly. *E.g.*, AlkemBr. 16, 17, 19, 21, 31, 36, 40, 42, 43. The court went on to spend several pages analyzing whether the '364 patent is obvious "***had*** a POSA chosen to study the crystal form of tapentadol hydrochloride." Appx142 (emphasis added). The district court's analysis as to a lack of motivation to select tapentadol hydrochloride for analysis is not grounds for clear error.

C. The '364 Patented Invention Was Not Obvious to Try

In the alternative, Alkem argues that it would have been obvious to try the techniques disclosed in the Byrn article to isolate and identify Form A of tapentadol hydrochloride. Alkem Br. 39-44. Alkem concedes that to prove "an invention was obvious to try [under *KSR*] means showing 'a design need or market pressure to solve a problem' ***and*** 'a finite number of identified, predictable solutions' to try." *Id.* at 39 (emphasis added) (quoting *KSR*, 550 U.S. at 421). Defendants nonetheless press forward with their argument that the '364 patented invention would have been obvious under this standard. When applied to the evidence, however, Alkem's argument falls apart.

Alkem's argument that there were a "finite number of predictable solutions for performing a polymorph screen" (AlkemBr. 41) is directly contrary to the district court's findings that "polymorph screening consists of an unpredictable application of . . . routine techniques," and that "the results of the polymorph

screen . . . would have been impossible to predict." Appx143-144. It is also contrary to the record in this case, which showed that there were almost an infinite number of experimental conditions and combinations that a person of ordinary skill could have explored in a polymorph screen. Appx10485-10486 (138:13-139:2); Appx10488-10490 (141:25-143:13); Appx57382-57407 at Appx57384 (Table 3). Byrn's broad general disclosure of a polymorph screen lacks any guidance as to the myriad of crystallization conditions that could be used to find a new polymorph of tapentadol hydrochloride, and the minor variations in preparative conditions that can produce a different crystalline result. Without any guidance in the art as to the specific conditions or combinations thereof to use or the potential result, the use of polymorph screening does not render Form A obvious. *See Takeda*, 2013 WL 9853725, at *68 ("there were [a] myriad [of] possible solvents, combinations of solvents, and adjustment of conditions (e.g., time and temperature [heating rates, cooling rates, evaporation rates, stirring, and seeding]) that could have been used to attempt to crystallize" the compound).

Both before and after *KSR*, this Court has consistently held that obvious to try does not render obvious a patented invention where the properties of an invention or the methods of obtaining it were not predictable, or where there was no reasonable expectation of success. In *In re O'Farrell*, this Court discussed two classes of situations where "obvious to try" is erroneously equated with

obviousness under 35 U.S.C. § 103, both of which apply with full force to Alkem's arguments here. 853 F.2d 894, 903 (Fed. Cir. 1988). The first situation is where a skilled artisan must "explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* Here, the record shows that the prior art (including Byrn) set forth only a general approach to conducting a polymorph screen with no guidance whatsoever on the particular form of the invention (Form A of tapentadol hydrochloride) or how to achieve it. Appx9627-9629 (97:13-99:11); Appx10789-10794 (213:20-218:24); Appx57372-57381; Appx57278-57324.

The second situation where obvious to try does not equate to obviousness is where "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d at 903. That is precisely the situation here, where the record showed that there were almost an infinite number of experimental conditions and combinations that a person of ordinary skill in the art could have explored in a polymorph screen. Appx10786 (210:8-22); Appx10789-10794 (213:20-218:24); Appx10485-10486 (138:13-139:2); Appx10488-10490 (141:25-

143:13); Appx57382-57407 at Appx57384 (Table 3); *see also Takeda*, 2013 WL 9853725, at *68.

Even in the case relied upon by Alkem, *In re Kubin*, this Court reaffirmed the above holdings from *In re O'Farrell* in view of *KSR*, cautioning against "erroneously equat[ing]" "obvious to try" with obviousness in the "two classes of situations" discussed above. 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d at 903). Thus, in *In re Armodafinil*, the court cited *In re Kubin* in ***rejecting*** the defendant's argument that it would be obvious to try experiments to prepare a particular polymorphic form, stating that "'[o]bvious to try' is not equivalent to obviousness in every case, particularly where, as here, the prior art provided at most general motivation to conduct trial and error experimentation in a decidedly unpredictable field." 939 F. Supp. 2d at 501-02 (citing *In re Kubin*, 561 F.3d at 1359-60); *see also Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008) ("The Court in *KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology.").

In subsequent decisions, this Court has continued to hold that obvious to try does not yield obviousness in situations like those discussed above. *See, e.g.*, *In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1376 (Fed. Cir. 2011) (rejecting "obvious to try" argument because the claimed invention would not have been an

expected result), *cert. denied*, 566 U.S. 905 (2012); *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1089 (Fed. Cir. 2008) (rejecting "obvious to try" argument where the district court made findings "on the unexpected and unpredictable properties" of the claimed compound).

In the specific context of polymorph patents, district courts have relied on these decisions in rejecting patent challengers' arguments that it would be "obvious to try" experiments to prepare a polymorph or polymorphs of the compounds at issue. *See, e.g., In re Armodafinil*, 939 F. Supp. 2d at 501 ("[D]efendants' contention based on allegedly 'obvious-to-try' experiments to prepare the most stable form of armodafinil falls short of proving that Form I would have been obvious."); *Takeda*, 2013 WL 9853725, at *68 ("[E]vidence that it would have been obvious to try to make all possible forms of dexlansoprazole and its enantiomers, including crystalline forms . . . does not suffice to establish obviousness.").

D. The District Court Did Not Require "Absolute Predictability"

Alkem's primary argument on appeal—that the district court erred in requiring "absolute predictability"—blatantly mischaracterizes both the district court's opinion and the law of obviousness. Nowhere did the district court state or imply that it was requiring absolute predictability; indeed, the language of the court's opinion shows the exact opposite. At the same time, Alkem's argument

completely ignores the wealth of precedent from this Court and the Supreme Court that predictability is a critical factor in the obviousness analysis. *KSR*, 550 U.S. at 421; *Eisai*, 533 F.3d at 1358-59; *DePuy Spine*, 567 F.3d at 1326.

As a preliminary matter, the district court explicitly acknowledged that "[o]bviousness ***does not*** require absolute predictability of success," but rather requires "a reasonable expectation of success." Appx89 (emphasis added) (citations omitted). Nothing in the district court's opinion suggests that it did not follow this standard. Instead, what the district court found was that the results of a polymorph screen in this case would have been "***impossible***" to predict. Appx143-144 (emphasis added); AlkemBr. 5-6, 16, 22-23 (citing the district court's "impossible to predict" finding as support somehow for the contention that "the district court erroneously relied upon a standard of absolute predictability"). Just because the results were not reasonably predictable or even predictable to some small extent does not mean that the court required "absolute predictability." Rather, the district court made a factual finding, based on all the evidence, that the results were not predictable at all—"impossible to predict." The district court did not err in holding the claims nonobvious based on well-established legal precedent. *KSR*, 550 U.S. at 421.

Alkem completely ignores the court's express findings and the law in arguing that the district court erred in its obviousness analysis. Tellingly, Alkem's

recitation of the "proper analysis" for obviousness omits predictability entirely when it declares that the inquiry is "whether there was a limited number of identified solutions." AlkemBr. 16-17. Noticeably absent is the actual language from the Supreme Court in *KSR*: whether "there are a finite number of identified, ***predictable*** solutions." 550 U.S. at 421 (emphasis added). Even more incredible, Alkem repeatedly faults the district court in "conclud[ing] for the polymorph patent that 'predictability is a touchstone of obviousness'" (AlkemBr. 23; *see also id.* at 16, 20), but that statement by the district court is a ***direct quote*** from this Court's decision in *DePuy Spine*, 567 F.3d at 1326. Alkem omits the citation to *DePuy Spine* each time it criticizes the district court's opinion. Appx144.

By mischaracterizing the district court's application and analysis of predictability, Alkem seeks to ignore the court's detailed factual findings that nothing about the '364 patent invention was predictable. *See* Appx142-144. But Alkem cannot pick and choose what aspects of the law or record that it likes and ignore the others. Alkem takes a similar, misguided approach with regard to motivation. While acknowledging its role in the legal analysis (AlkemBr. 16-17), Alkem ignores the district court's discussion of the various cases in which other district courts rejected the "conten[tion] that a POSA would have been motivated to discover the claimed polymorph." *See, e.g.*, Appx144 (citing cases). In particular, the district court highlighted the statement by the District of Delaware in

In re Armodafinil that "for a patent challenger to establish obviousness, it is insufficient to allege a general motivation to discover an undefined solution that could take many possible forms." *Id.* (citing 939 F. Supp. 2d at 500). The district court also recited this Court's statement in *Innogenetics, N.V. v. Abbott Laboratories* that "knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method." Appx144-145 (citing 512 F.3d 1363, 1373-74 (Fed. Cir. 2008)).

With regard to the "reasonable expectation of success," the district court stated that "[o]bviousness does not require absolute predictability of success," but rather requires "a reasonable expectation of success." Appx89 (citations omitted). Although the court did not explicitly discuss "expectation of success" in the context of obviousness, as discussed above, there is an inextricable link between whether there would have been a "reasonable expectation of success" and predictability, including whether the experiments required are predictable or involve trial and error. *See, e.g.*, *Pfizer*, 555 F. App'x at 971; *Merck*, 125 F. Supp. 3d at 514. At trial, Plaintiffs presented evidence that polymorphism testing involved unpredictable, "trial-and-error" experiments. Appx9767-9769 (45:21-47:6); Appx10786-10797 (210:8-221:11). The district court found that there are "a large variety of conditions that could be appropriate for a particular polymorph screen," and as a result, "there is no way to know how a screen will proceed before

beginning to experiment . . . ." Appx143. These findings are more than sufficient to support a finding of no reasonable expectation of success.

E. The District Court Did Not Create a Rule that Polymorph Patents Can Never Be Obvious

Alkem's contention that the district court created "an improper rule that polymorph patents can never be obvious" (AlkemBr. 19) is irrelevant hyperbole. The district court explicitly stated that it "does not speak on the hypothetical question of whether every polymorph patent is nonobvious" (Appx145); it certainly did not state that patent claims directed to polymorphs can never be obvious. Nor did it make any findings that would compel that conclusion. The district court's decision was narrowly tailored to the specific crystalline form of the compound claimed in the '364 patent in view of the specific prior art in this case, and does not address the possibility that other polymorphs may be obvious.

In this case, for example, the prior art set forth only a general approach to conducting a polymorph screen with no guidance whatsoever on the particular form of the invention (Form A of tapentadol hydrochloride) or how to achieve it. Appx9627-9629 (97:13-99:11); Appx10785-10797 (209:14-221:11); Appx57372-57381; Appx57278-57324. In other cases, there may be prior art references that would give a person of ordinary skill a reasonable expectation of success for a finite number of identified, predictable solutions. But that was not the state of the art in 2004 with respect to tapentadol hydrochloride. In cases such as this one,

where a skilled artisan must explore a "general approach" or where the prior art gave only "general guidance" as to the form of the claimed invention or how to achieve it, this Court has rejected Alkem's "obvious to try" argument. *See supra* Argument Section I.C.

Moreover, in this case, nothing whatsoever was known about the crystalline landscape of tapentadol hydrochloride. *See* Appx143-144 ("[T]he determination of the structure and properties of the polymorph forms of ***tapentadol hydrochloride***—would have been impossible to predict." (emphasis added)). As such, there was no basis to believe, for example, that tapentadol hydrochloride was polymorphic. *See* Appx142 ("Had a POSA specifically decided to screen for polymorphs of tapentadol hydrochloride, a POSA would not have been able to look at the structure of tapentadol hydrochloride and predict whether it is polymorphic." (citing 3/10 Tr. (Gruss) [Appx8837] at 267:13-21; 3/21 Tr. (Bernstein) [Appx10782] at 206:3-7; 3/16 Tr. (Steed) [Appx9772] at 50:15-20)). In short, Alkem's dire predictions regarding the effect of the district court's opinions on future cases are simply baseless and irrelevant speculation.

As it did in the district court, Alkem once again attempts to "discredit [Plaintiffs' expert] Dr. Bernstein's testimony by noting his expert opinion that 'no polymorph patent can ever be obvious.'" Appx145; AlkemBr. 20. Dr. Bernstein is a scientist, not a lawyer, and this broad statement was based on his scientific, not

legal, expertise. Clearly, Dr. Bernstein has not applied and was not applying the legal principles of obviousness to every possible polymorph. Having had the opportunity to examine Dr. Bernstein and weigh his credibility, the district court in this case (as in other cases in which Dr. Bernstein testified) credited Dr. Bernstein and the additional evidence in the record regarding the polymorphs of the particular compound at issue in finding that the asserted claims were not obvious. Alkem has not shown that any of the district court's factual findings are clearly erroneous, or that the district court legally erred in reaching its conclusion.

F. Alkem's Cited Cases Do Not Render the Claims Obvious

Instead of meaningfully discussing or trying to distinguish the many similar cases that have found polymorph patents valid and nonobvious, Alkem relies on cases completely outside the polymorph context, which are inapposite and factually distinguishable. For example, Alkem states that in *Pfizer v. Apotex*, this Court held that "***[i]n the salt context***, patent claims are invalid as obvious where a company screens commonly known anions . . . using routine techniques and then claims one that works." Alkem Br. 6 (emphasis added) (citing 480 F.3d at 1367-69). In contrast to this case, in *Pfizer*, the Court recognized that the prior art not only provided "ample motivation to narrow the [prior art] genus of 53 pharmaceutically-acceptable anions . . . to a few [species]," but also "predicted the results, which Pfizer merely had to verify." 480 F.3d at 1363, 1367. Here, the art

and evidence of record explicitly recognizes that unlike the formation of salts, the formation of polymorphs is unpredictable. Appx57382-57407 at Appx57403 ("Unlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of hydrates, solvates, co-crystals and polymorphs have defied prediction."); *see also* Appx9772-9773 (50:15-51:10); Appx10557 (210:8:22); Appx143-144; Appx10773-10777 (197:15-201:19); Appx10779-10782 (203:2-206:7); Appx10794-10795 (218:11-219:20).

Likewise, in *AstraZeneca LP v. Breath Ltd.*, Alkem states that this Court held that "***[i]n the sterile compound context***, patent claims are invalid as obvious where a company selects from ***known sterilization techniques which simply claims a particular result***." Alkem Br. 6 (emphases added) (citing 603 F. App'x 999, 1002 (Fed. Cir. 2015)). Unlike the many methods for investigating polymorphism presented in this case, there was no evidence in *AstraZeneca* that the five well-known, well-established sterilization techniques were unpredictable or required trial and error, in stark contrast to the unpredictability of a polymorph screen. 603 F. App'x at 1001-02.

In *Cubist Pharmaceuticals, Inc. v. Hospira, Inc.* (AlkemBr. 6-7, 26-27), the claims at issue were method or product-by-process claims that specifically required using obvious, well-known purification techniques to obtain a purified version of

the starting product. 805 F.3d 1112, 1127-28 (Fed. Cir. 2015). Here, the claims are directed to a previously unknown and unpredictable crystalline structure of a compound, not a well-established method of making it.

Finally, in *Santarus, Inc. v. Par Pharmaceutical, Inc.* (AlkemBr. 35), the composition ***itself*** was found obvious over the prior art, such that the claimed, resulting blood serum concentrations achieved from administering that composition were also held to be obvious. 694 F.3d 1344, 1353-54 (Fed. Cir. 2012). Here, Form A of tapentadol hydrochloride was neither taught nor suggested by the prior art, and was not an "obvious composition" whose inherent properties were then measured and claimed.

In a last futile attempt to attack the district court's holding, Alkem argues that "the lack of secondary considerations" with respect to the '364 patent "confirms the obviousness of the asserted polymorph claims." AlkemBr. 38-39. Once again, that is not the law. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985) ("[E]vidence of secondary considerations need not be necessarily conclusive on the obviousness/nonobviousness issue."); *Leinoff v. Louis Milona & Sons, Inc.*, 726 F.2d 734, 740 (Fed. Cir. 1984) ("The so-called secondary considerations . . . are simply indicia of nonobviousness. . . . Although this evidence often helps a tribunal determine an invention's nonobviousness, it is not necessarily conclusive."), *overruled on other grounds by*

A.C. Aukerman Co. v. R.L. Chaides Const. Co., 960 F.2d 1020 (Fed. Cir. 1992). Given that Defendants did not establish a prima facie case of obviousness below, Plaintiffs were not required to rebut Defendants' assertions with objective indicia of nonobviousness. *Winner Int'l Royalty*, 202 F.3d at 1350 ("Because [defendant] failed to establish a prima facie case of obviousness, however, [patentee] was not required to establish commercial success.").

In light of Alkem's inability to establish a prima facie case of obviousness, the district court correctly held that the '364 patent is not invalid for obviousness.

II. The District Court Correctly Held that the Asserted Claims of the '364 Patent Are Not Invalid for Lack of Utility

To satisfy the utility requirement, one must "show that an invention is useful to the public as disclosed in its current form" and "disclose a use which is not so vague as to be meaningless." *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). "The threshold of utility is not high: [a]n invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999) (citations omitted). To violate 35 U.S.C. § 101, "the claimed device must be '***totally incapable*** of achieving a useful result.'" *Id.* (emphasis added) (quoting *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992)). Contrary to West-Ward's suggestion (West-WardBr. 29), *In re Selmi*, 156 F.2d 96 (C.C.P.A. 1956) does not teach that utility requires something "new" or "different" than that of the art of

record. *See also Demaco Corp.*, 851 F.2d at 1390 ("The patent statute does not require that a patentable invention be superior to all prior devices.").

The district court found two distinct bases for the utility of the '364 patent. First, the court found that the '364 patent discloses that Form A of tapentadol hydrochloride is useful for treating pain. Appx146 (citing '364 patent at 1:42-45 [Appx397]) (explaining that the patent provides "new solid forms of [tapentadol hydrochloride] useful in the treatment or inhibition of pain"). As the court explained, "[t]he '364 patent explicitly references the '737 patent, which teaches that tapentadol hydrochloride is useful for treating pain." *Id.* (citing '364 patent at 1:46 [Appx397]). The court also noted that in 2004, it was generally known in the art that tapentadol hydrochloride was useful as an analgesic. *Id.* (citing DTX-260_0072 [Appx58057-58147 at Appx58128]; 3/22 a.m. Tr. (Bernstein) at 20:12-21:7 [Appx10897-10898]). Indeed, there is no dispute that tapentadol hydrochloride is useful for treating pain. Appx146; Appx9843 (121:15-17); Appx10897-10898 (20:12-21:7). Contrary to West-Ward's suggestion (West-WardBr. 37), the court correctly determined that there was utility as of the filing date, without relying on "what is *now* known about a pharmaceutical compound."

On appeal, West-Ward argues that the court cannot rely on the fact that the '737 patent teaches that tapentadol hydrochloride is useful for treating pain because the '364 patentees claimed a new Form A of tapentadol hydrochloride

which is different from the Form B that was disclosed in the '737 patent, and that "the generally known analgesic properties of [the] tapentadol hydrochloride structure could not . . . establish the substantial utility of the new Form A." West-WardBr. 36. But the '364 patent explains that "Form A has the same pharmacological activity as Form B." Appx398 (4:14-16). A person of ordinary skill would have no reason whatsoever to doubt this statement, as Form A has the identical chemical structure to the tapentadol hydrochloride disclosed in the '737 patent; it is only the crystalline structure that is different. But when tapentadol hydrochloride is dissolved, for example in the gastric fluid of the stomach, no crystal structure remains. Appx8476 (176:18-21); Appx10568-10569 (221:19-222:4) ("it doesn't matter which form it was to begin with"). The analgesic properties of the compound tapentadol hydrochloride remain the same whether it starts as Form A or B.

Thus, this case is unlike the cases upon which West-Ward relies (West-WardBr. 28-29, 36-37). For example, in *Brenner v. Manson*, the court found that the respondent did not show "sufficient likelihood that the steroid yielded by his process would have similar tumor-inhibiting characteristics" to a steroid's adjacent homologue where "respondent himself recognized that the presumption that adjacent homologues have the same utility has been ***challenged*** in the [relevant] field." 383 U.S. 519, 532 (1966) (emphasis added). Likewise, in *In re Kirk*, 376

F.2d 936, 942 (C.C.P.A. 1967) (West-WardBr. 29, 30, 36), the patentees attempted to import activity from one molecule to another. Here, however, there is no dispute that tapentadol hydrochloride was known to be useful for treating pain as of the priority date of the '364 patent.

Relying on *Parker v. Flook*, 437 U.S. 584 (1978), West-Ward argues that the district court's finding of no anticipation is inconsistent with its finding that Form A has utility in light of its usefulness as an analgesic. West-WardBr. 36-37. But anticipation and utility are distinct legal issues, relying on distinct underlying facts. And *Parker* is inapposite—it deals with subject matter eligibility, not utility or anticipation. *See, e.g.*, 437 U.S. at 587.

In addition to being useful for treating pain, the court also found that the '364 patent discloses that Form A "is more stable under ambient conditions" than Form B. Appx147 (quoting Appx398 (4:13-17)). West-Ward argues, as Defendants did below, that the statement of utility in the '364 patent is vague and that certain terms are not defined. West-WardBr. 5, 26, 38-42. The district court concluded, however, that it "understands these terms the same way all of the [fact and expert] witnesses appeared to understand the terms—that Form A is the form that tends to persist (and that Form B will tend to convert to Form A) at room temperature." Appx147 (citing 3/15 Tr. (Steed) at 234:3-6 [Appx9605-9606

(75:23-76:1)]; 3/16 Tr. (Matzger) at 107:6-11 [Appx9829]; 3/21 Tr. (Bernstein) at 268:3-6 [Appx10844]; 3/10 Tr. (Gruss) at 226:14-18 [Appx8796]).

West-Ward argues that a person of ordinary skill in the art "could never accept" this assertion "'without question' as 'obviously correct' and would demand experimental proof of such claimed utility." West-WardBr. 5 (citing *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323-24 (Fed. Cir. 2005)). West-Ward's argument is flawed for several reasons. Most fundamentally, it is based on the false premise that there "are no data disclosed" in the '364 patent to support the notion that Form A is more stable than Form B. *Id.* at 26; *see also id.* at 5-6, 17, 34-35. But, as the district court found, "Example 16 of the '364 patent," which sets forth a variable temperature XRPD experiment, demonstrates that "Form A is more stable at room temperature" than the previously known Form B. Appx148. The court noted that even Defendants' expert, "Dr. Steed[,] agreed with this conclusion; he concluded from Example 16 that Form A and Form B are an 'enantiotropic pair,' with Form A being stable at room temperature and Form B being stable at higher temperatures." Appx148 (citing 3/15/16 Tr. (Steed) at 234:13-235:21 [Appx9606-9607 (76:12-77:16)]); *see also* Appx10471-10472 (124:9-125:6). Indeed, the evidence in this case is undisputed that Form A is more thermodynamically stable than Form B at room temperature. Appx9829 (107:5-11); Appx9844 (122:17-25); Appx10471 (124:9-13).

West-Ward's complaint that Example 16 does not disclose the exact threshold temperature that Form B changes over into Form A (West-WardBr. 39-40) does not remove the utility of the invention. Example 16 discloses that the point of transition or phase change from Form A to Form B occurs at a temperature between 40 and 50ºC. The record showed that a person of ordinary skill would understand from this that at temperatures ***below*** 40ºC, Form A is the more thermodynamically stable form. Appx10471-10472 (124:9-125:6); Appx9694-9696 (57:24-59:7). West-Ward's argument to the contrary is once again contradicted by the testimony of its own expert, Dr. Steed, who reviewed Example 16 and concluded on the same data that ***Form A was stable at room temperature***. Appx9694-9696 (57:24-59:7).

West-Ward's assertion that Example 16 means that for the '737 patent examples to yield Form B, "the tapentadol hydrochloride disclosed in the '737 patent were maintained in an oven" and the "writhing test on mice described in the '737 patent were performed in equally sauna-like conditions with equally scalding-hot formulations of tapentadol hydrochloride" (West-WardBr. 40-41), is as false as it is ridiculous. It is undisputed that Form B is metastable at room temperature and that it can persist at room temperature for years, even if it is not the most thermodynamically stable form at that temperature. Appx10818-10819 (242:2-243:22); Appx9829-9830 (107:20-108:4); Appx9831-9832 (109:24-110:3);

Appx9614-9616 (84:3-86:2); Appx9730 (8:19-22); Appx9730-9731 (8:23-9:16); Appx10820-10823 (244:14-247:1). There was ample evidence at trial that Form B can exist for years at temperatures below 40 to 50ºC. Appx10818 (242:12-21); Appx10819 (247:23-248:1); Appx8538-8539 (238:20-239:7); Appx8542-8544 (242:5-244:22); Appx9730-9731 (8:19-9:23); Appx10820-10823 (244:14-247:1); Appx48929-48931; Appx48932-48935; Appx47940-47944; Appx47945-47950; Appx48957-48958. Indeed, Dr. Buschmann's original synthesis of tapentadol hydrochloride subsisted for almost eight years before it was tested and determined to be Form B. Appx8543-8544 (243:19-244:22); Appx8555-8556 (255:24-256:12); Appx9730-9731 (8:23-9:16); Appx10820-10823(244:14-247:1). No oven or sauna-like conditions were required for Example 25 of the '737 patent to yield Form B.

Second, West-Ward is incorrect that a person of ordinary skill would not accept "without question" that Form A is more stable than B. West-WardBr. 5 (citing *Rasmusson*, 413 F.3d at 1323). In *Rasmusson*, which provides the foundation of West-Ward's utility argument, the court limited its holding to "the context of determining whether sufficient 'utility ***as a drug, medica[ment]***, and the like in human therapy' has been alleged." 413 F.3d at 1323 (emphasis added) (citation omitted). There, this Court agreed with the Board of Patent Appeals and Interferences that a person of ordinary skill in the art would not have simply

believed that the novel compound at issue was effective in treating prostate cancer without more. *Id.* at 1324. Likewise, *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996) (West-WardBr. 34) also addressed utility in the context of a novel compound. This case presents a very different context. Here, the person of ordinary skill is not presented with a new drug or medicament, but with a new crystalline structure of a drug that has already been described and tested. A person of ordinary skill in the art would certainly find it believable that a new polymorphic form discovered is more stable than its predecessor form. Indeed, Plaintiffs' expert, Dr. Bernstein, explained at trial that "if" new polymorphic forms of a compound appear, it is ***likely*** that they would be more stable than previous forms. Appx10782-10783 (206:12-207:5).

As this Court held in *In re Fisher*, "to [s]atisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." 421 F.3d at 1371. Form A indisputably has such a benefit—it is being used as an analgesic by hundreds of thousands of NUCYNTA® patients, and Defendants seek to use it in their own products. Moreover, it is the increased stability of Form A under ambient conditions as compared to the previously known Form B that enables the drug to be successful in the marketplace without the need for controlling temperatures to

avoid form conversion. These disclosed benefits of Form A are undeniably sufficient to satisfy the utility requirement. *Id.*; *Juicy Whip*, 185 F.3d at 1366.

CONCLUSION

The district court correctly held that Defendants failed to establish by clear and convincing evidence that the asserted claims of the '364 patent are invalid. The court's judgment of no invalidity should be affirmed.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on December 1, 2017, true and correct copies of RESPONSE BRIEF OF CROSS-APPELLANT GRÜNENTHAL GMBH were served upon registered counsel by operation of the Court's CM/ECF system.

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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 13,605 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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