United States Court of Appeals for the Federal Circuit

GRUNENTHAL GMBH, ASSERTIO THERAPEUTICS, INC.,
Plaintiffs-Cross-Appellants

v.

ALKEM LABORATORIES LIMITED, HIKMA PHARMACEUTICALS INTERNATIONAL LIMITED, HIKMA PHARMACEUTICALS USA INC.,
Defendants-Appellants

ACTAVIS ELIZABETH LLC,
Defendant-Appellee

ACTAVIS LABORATORIES UT, INC.,
Defendant

2017-1153, 2017-2048, 2017-2049, 2017-2050

Appeals from the United States District Court for the District of New Jersey in 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.

Decided: March 28, 2019

MICHAEL SITZMAN, Gibson, Dunn & Crutcher LLP, San Francisco, CA, argued for all plaintiffs-cross-appellants. Plaintiff-cross-appellant Assertio Therapeutics, Inc. also represented by JAYSEN CHUNG; CHRISTINE RANNEY, Denver, CO; TIMOTHY P. BEST, Los Angeles, CA.

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IMRON T. ALY, Schiff Hardin, Chicago, IL, argued for defendant-appellant Alkem Laboratories Limited. Also represented by CINDY AHN, JASON HARP, NEIL LLOYD; AHMED M.T. RIAZ, New York, NY.

Before REYNA, TARANTO, and CHEN, *Circuit Judges.*

REYNA, *Circuit Judge.*

Alkem Laboratories Limited, Hikma Pharmaceuticals International Limited, and Hikma Pharmaceuticals USA Inc. appeal the judgment of the district court that U.S. Patent No. 7,994,364 is not invalid for obviousness or lack of utility. Grünenthal GmbH and Assertio Therapeutics, Inc., formerly Depomed, Inc., cross-appeal the finding that Hikma Pharmaceuticals International Limited, Hikma Pharmaceuticals USA Inc., and Actavis Elizabeth LLC do

not infringe U.S. Patent No. 8,536,130. Because the district court did not err in its conclusions, we affirm.

BACKGROUND

A. Patents at Issue

Grünenthal GmbH ("Grünenthal") is the assignee of U.S. Patent Nos. 7,994,364 ("the '364 patent") and 8,536,130 ("the '130 patent"). Assertio Therapeutics, Inc., formerly Depomed, Inc. ("Depomed"), is an exclusive licensee of both patents. Each patent is listed in the U.S. Food and Drug Administration's ("FDA") *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") for NUCYNTA® ER (extended release), a tapentadol hydrochloride tablet. J.A. 52853, 52856. The '364 patent is directed to the Form A polymorph[1] of the chemical compound tapentadol hydrochloride and a method of treating pain and/or urinary incontinence.[2] *See* '364 patent, Abstract; *id.* col. 18 l. 66–col. 19 l. 4. The '364 patent states that Form A "is very stable at ambient conditions and therefore useful for producing a pharmaceutical composition." *Id.* col. 1 ll. 63–67. The asserted claims of the '364 patent, claims 1, 2, 3, and 25, recite various X-ray powder diffraction (XRPD) patterns. *See, e.g.*, *id.* col. 18 l. 65–col. 19 l. 4. XRPD is a method for measuring the X-rays scattered by a polycrystalline sample as a function of scattering angle. Each polymorph has a unique XRPD.

The '130 patent describes a method of using tapentadol and tapentadol hydrochloride for the treatment of polyneuropathic pain. Polyneuropathic pain is a type of pain

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[1] A polymorph is a chemical compound that can present in different three-dimensional crystalline structures.

[2] The patent claims "(–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride," which is tapentadol hydrochloride. '364 patent, col. 18 ll. 66–67; *see also* Grünenthal Br. 8.

caused by damage to multiple nerves. In contrast, mononeuropathic pain is pain associated with damage to a single nerve.

Claim 1 of the '130 patent is directed to the method of treating "polyneuropathic pain" with tapentadol or "a pharmaceutically acceptable salt thereof," i.e., tapentadol hydrochloride. '130 patent, col. 18 ll. 2–7. Claim 2 is directed to the method of treating polyneuropathic pain using "a hydrochloric salt" of tapentadol, i.e., tapentadol hydrochloride. *Id.* col. 18 ll. 8–10.

B. Prior Art References

There are two different polymorphs of tapentadol hydrochloride: Form A and Form B. Form B of tapentadol hydrochloride was known in the art and previously disclosed in U.S. Patent No. 6,248,737 ("the '737 patent"), also assigned to Grünenthal. *See* '364 patent, col. 1 ll. 58–63. The '737 patent discloses a number of compounds, including tapentadol hydrochloride, intended to have an analgesic effect suitable for the treatment of pain. *See, e.g.*, '737 patent, col. 1 l. 52–col. 2 l. 36; *id.*, Example 25, col. 20 ll. 1–20.[3] Specifically, Example 25 of the '737 patent discloses the steps for synthesizing tapentadol hydrochloride. The '737 patent states that tapentadol hydrochloride was crystallized, but it does not describe the resulting crystal structure, nor does it discuss polymorphs.

Also known in the art at the time of filing was the concept of polymorph screening, which is the practice of characterizing all crystal forms of a chemical compound. A

[3] Example 25 incorporates by reference the synthesis steps of Example 24 and the synthesis preparation process of Example 2 of the '737 patent. '737 patent, col. 20 ll. 18–20.

1995 article by Byrn et al.[4] ("Byrn") "describes a conceptual approach to the characterization of pharmaceutical solids," including a flow chart describing investigative steps to determine whether polymorphs are possible. J.A. 57372–73. Byrn does not outline a particular method to definitively test for polymorphism.[5] Instead, it provides a decision tree outlining, among other things, different ways to gain additional information about whether polymorphs exist for a particular chemical compound and lists various analytical tests to identify polymorphs. J.A. 57373.

To determine whether polymorphs are possible, Byrn lists a number of solvents to be used in recrystallizing the substance in question. The listed solvents are water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, and hexane. *Id.* Other variables such as temperature, concentration, agitation, and pH could affect the solids produced by recrystallization with these various solvents. *Id.*, Figure 1. This case focuses on the extent and limits of what the disclosure in Byrn teaches about discovering polymorphs, if any, of a known compound, and ultimately, whether a skilled artisan would reasonably expect the recrystallization of tapentadol hydrochloride to result in any polymorph, let alone one with the physical properties of Form A.

C. Proceedings in District Court

Grünenthal and Depomed (collectively, "Cross-Appellants") brought suit against Alkem Laboratories Limited

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[4] Stephen Byrn et al., *Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*, 12 Pharmaceutical Res. 945 (1995).

[5] Polymorphism is the ability of a compound to crystallize in more than one crystal arrangement but retain the same chemical structure. J.A. 8528 (228:11–14); J.A. 57373.

("Alkem"), Hikma Pharmaceuticals International Limited,[6] Hikma Pharmaceuticals USA Inc. (collectively, "Hikma"), and Actavis Elizabeth LLC ("Actavis"),[7] alleging infringement of the '364 and '130 patents stemming from their respective Abbreviated New Drug Application ("ANDA") filings seeking to market generic versions of immediate and extended release tapentadol hydrochloride tablets.[8] All defendants subsequently stipulated to infringement of the '364 patent. Alkem and Hikma challenged the validity of the '364 and '130 patents.

After a bench trial, the district court concluded that Alkem infringes the '130 patent, but that Actavis and Hikma do not. *In re Depomed Patent Litig.*, No. 13-cv-4507-CCC-MF, 2016 WL 7163647, at *2 (D.N.J. Sept. 30, 2016) ("*Depomed Litigation*"). The district court also determined that the '364 patent is not invalid as obvious, that the '130 patent is not invalid as anticipated, and that the '130

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[6] Hikma Pharmaceuticals International Limited was formerly known as West-Ward Pharmaceuticals International Limited. During pendency of this appeal, defendant Roxane Laboratories, Inc. ("Roxane") transferred ownership of its ANDA applications, which are at issue in the instant appeal, to West-Ward Pharmaceuticals International Limited. ECF No. 65. As a result, West-Ward Pharmaceuticals International Limited was substituted for Roxane in this appeal. ECF No. 66.

[7] Grünenthal and Depomed also brought suit against Actavis Laboratories UT, Inc., Actavis LLC, and Actavis, Inc. These defendants did not participate in this appeal.

[8] U.S. Patent Nos. RE39,593 and 8,309,060 were also asserted. J.A. 33. U.S. Patent No. RE39,593 is not directly at issue in this appeal, but Hikma relies on it for purposes of its invalidity arguments. The proceedings involving U.S. Patent No. 8,309,060 were stayed by the district court. *Id.*

patent is not invalid due to obviousness-type double patenting in light of U.S. Patent No. RE39,593. *Id.*

Alkem and Hikma each appeal different aspects of the district court's invalidity rulings. Grünenthal and Depomed collectively appeal the district court's finding of noninfringement of the '130 patent. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Much of Hikma's argument on appeal is made in the alternative and many of its arguments become moot should we hold Hikma does not infringe the '130 patent. Therefore, we will first address Cross-Appellants' arguments regarding noninfringement. We will then address Alkem's appeal of the finding that the '364 patent is not invalid as obvious and Hikma's challenge to the utility and validity of the '130 patent.

A. Infringement

We begin with a discussion of Grünenthal and Depomed's cross-appeal. Because neither Hikma's nor Actavis's proposed label is indicated to treat polyneuropathic pain, and the case made by Grünenthal and Depomed for indirect infringement depended on the proposed label indications, we agree with the trial court that Hikma and Actavis do not induce infringement of or contributorily infringe claims 1 and 2 of the '130 patent.

Depomed has several NUCYNTA® products used "for the management of moderate to severe acute pain in adults." *See* J.A. 70–73. One of Depomed's products, NUCYNTA® ER (extended release), is a tablet approved for the following indications:

> NUCYNTA® ER is an opioid agonist indicated for the management of:
>
> - moderate to severe chronic pain in adults

- ***neuropathic pain*** associated with diabetic peripheral neuropathy (DPN) in adults

when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

J.A. 50091 (emphasis added, reference numerals omitted). The label makes no explicit reference to "polyneuropathic pain," but DPN is a type of polyneuropathic pain. Depomed Br. 18, 20. The original label for NUCYNTA® ER did not include the second indication to treat neuropathic pain. J.A. 50310.

Hikma and Actavis each filed ANDAs seeking approval to market a generic version of tapentadol hydrochloride extended release tablets. Both parties filed "Section viii" statements under 21 U.S.C. § 355(j)(2)(A)(viii), whereby Hikma and Actavis told FDA that they will not seek FDA approval for an indication directed to the treatment of DPN. J.A. 7290–91; *see also* J.A. 52858.

Induced Infringement

After a bench trial, this court reviews a district court's judgment for legal error or clearly erroneous findings of fact. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1337 (Fed. Cir. 2005). Infringement is a question of fact reviewed for clear error. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010) (quoting *Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1361 (Fed. Cir. 2006)) (internal quotation marks omitted); *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1186 (Fed. Cir. 2014). A finding is clearly erroneous when "the reviewing court is left with the definite and firm conviction that a mistake has been made." *AstraZeneca*, 633 F.3d at 1056.

In this case, the question of induced infringement turns on whether Hikma and Actavis have the specific intent, based on the contents of their proposed labels, to encourage physicians to use their proposed ANDA products to treat polyneuropathic pain. *See Takeda Pharm. U.S.A., Inc. v.*

West-Ward Pharm. Corp., 785 F.3d 625, 631 (Fed. Cir. 2015). In other words, we ask whether the label encourages, recommends, or promotes infringement. *Id.* Depomed argues that because the Hikma and Actavis labels contain an indication for severe chronic pain, the labels will cause at least some users to infringe the '130 patent because polyneuropathic pain is a common form of "severe chronic pain." Depomed Br. 61–62.

"The pertinent question is whether the proposed label instructs users to perform the patented method." *AstraZeneca*, 633 F.3d at 1060. In this case, we ask whether the Hikma and Actavis labels instruct users to treat polyneuropathic pain with tapentadol hydrochloride. They do not.

Actavis's proposed ANDA product is indicated for "[p]ain severe enough to require daily, around-the-clock, long-term opioid treatment." J.A. 52679. Hikma's proposed ANDA product has a similar indication, designated for "[m]oderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." J.A. 56864–65; *see also* Hikma Br. 23. To support these indications, the Hikma and Actavis proposed labels cite chronic lower back pain studies, a type of pain that both Cross-Appellants and FDA defined as nociceptive.[9] At trial, experts on both sides testified that severe chronic pain could be neuropathic pain or nociceptive pain. *E.g.*, J.A. 9190 (169:9–17); J.A. 9388 (40:15–22); J.A. 9389 (41:19–23); J.A. 9399 (51:20–22); J.A. 10630 (54:2–8); J.A. 11161 (12:4–14); J.A. 11208 (59:13–20). In other words, even if severe chronic pain includes polyneuropathic pain, it also includes mononeuropathic pain and nociceptive pain. Therefore, the proposed ANDA labels do

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[9] Nociceptive pain is pain associated with damage to non-neural tissue, or non-nerve tissue.

not specifically encourage use of tapentadol hydrochloride for treatment of polyneuropathic pain.

Further, it is undisputed that neither of the accused ANDA labels list an indication for the management of pain associated with DPN. Nor do they mention any DPN clinical studies, which served as the basis for FDA approval of NUCYNTA® ER's indication for the treatment of neuropathic pain. In fact, both Hikma and Actavis filed "Section viii" statements with FDA specifically carving out the neuropathic pain indication. Accordingly, we agree with the district court that these labels do not encourage infringement of the '130 patent. *See Takeda*, 785 F.3d at 631 ("The label must encourage, recommend, or promote infringement.").

Cross-Appellants rely heavily on the holding in *AstraZeneca LP v. Apotex, Inc.*, where we held that if the label instructs "at least some users" to infringe the patent, then specific intent to induce infringement may be inferred. 633 F.3d at 1059–60. But *AstraZeneca* is inapposite to our facts. We held that specific intent could be inferred because the defendant proceeded with a plan to distribute the generic drug knowing that its label posed infringement problems. *Id.* In addition, the instructions in the DOSAGE AND ADMINISTRATION section of the label "would inevitably lead some consumers to practice the claimed method" of once-daily dosing by encouraging users to taper downward to the "lowest effective dose" and showing the lowest effective dose to be the lowest available strength, administered daily. *Id.* at 1057, 1059–60. Here, Grünenthal and Depomed point only to the indications of the proposed labels as grounds for inducement, which, as explained above, do not implicitly or explicitly encourage or instruct users to take action that would inevitably lead to use of tapentadol hydrochloride for treatment of polyneuropathic pain. Therefore, we discern no clear error and uphold the district court's finding of no induced infringement.

Contributory Infringement

To establish liability for contributory infringement, a patent owner must show, *inter alia*, that there are no substantial noninfringing uses for the accused product. 35 U.S.C. § 271(c). A noninfringing use is substantial when it is "not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1362 (Fed. Cir. 2012) (quoting *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009)). In a pharmaceutical case, the noninfringing use must be in accordance with the use for which the product is indicated. *Eli Lilly and Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 927 (Fed. Cir. 2011) ("[U]nauthorized activity does not avoid infringement by a product that is authorized to be sold solely for the infringing use.").

The question before us is whether the noninfringing uses Hikma and Actavis identified for the district court are "substantial." Cross-Appellants argue that any non-infringing uses for the proposed ANDA products are "rare" and not substantial. Depomed Response Br. 74. We disagree and find no clear error in the district court's finding that Hikma and Actavis do not contributorily infringe the '130 patent.

The district court weighed the testimony of all experts in this case, giving due consideration to both Cross-Appellants' and Appellants' experts. Cross-Appellants' experts opined that most of the uses of the proposed ANDA products would be directed to chronic, polyneuropathic pain. Appellants' experts, some of whom included practicing physicians, provided testimony about the use of tapentadol hydrochloride in their respective practices, including statements that they have prescribed opioids to treat severe chronic pain conditions that are nociceptive or not polyneuropathic. They testified that treating nociceptive or mononeuropathic conditions with tapentadol hydrochloride would not be unusual. Although there appears to be

evidence supporting both positions, the court made credibility determinations that supported Hikma and Actavis's theory of noninfringement. We see no reason to disturb those findings. *See Nilssen v. Osram Sylvania, Inc.*, 504 F.3d 1223, 1231–32 (Fed. Cir. 2007) ("While an opposite conclusion could have been reached, it is not the function of a court of appeals to override district court judgments on close issues, where credibility findings have been made."); *Agfa Corp. v. Creo Prods. Inc.*, 451 F.3d 1366, 1379 (Fed. Cir. 2006) ("This court must defer heavily to the trial court's credibility determinations.").

B. Obviousness

Obviousness is a question of law with underlying factual findings related to, among other things, the scope and content of the prior art, whether a person of ordinary skill in the art ("POSA") would have had reason to combine or modify the prior art to arrive at the claimed invention, and in so doing, would have had a reasonable expectation of success. *IXI IP, LLC v. Samsung Elecs. Co., Ltd.*, 903 F.3d 1257, 1262 (Fed. Cir. 2018); *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1371 (Fed. Cir. 2018).

On appeal, Alkem argues that, at least because of FDA guidance suggesting the undertaking of polymorph screenings for pharmaceutical solids, the district court clearly erred in finding no motivation to combine. We need not address that challenge because Alkem acknowledges that it also had to prove a reasonable expectation of success in arriving at Form A or, relatedly, it would have been obvious to try to find a polymorph of Form B of tapentadol hydrochloride. Based on the district court's findings of fact, we conclude that Alkem has not met those standards. Consequently, we reject the challenge to the district court's holding that Alkem failed to prove obviousness.

Reasonable Expectation of Success

The district court did not clearly err in finding that a POSA would not have had a reasonable expectation of successfully producing Form A, as claimed in the '364 patent, by using the methods outlined in Byrn on the compound disclosed in the '737 patent (Form B). As an initial matter, polymorphism of tapentadol hydrochloride was unknown at the time of filing the '364 patent. Form B was the only crystal structure of tapentadol hydrochloride known in the art at the time. *See* J.A. 8567 (267:13–21); 9772–73 (50:11–51:10). As the record reflects, polymorphism does not occur in all compounds. *Depomed Litigation*, 2016 WL 7163647, at *51 ("Dr. Bernstein testified that about 30 to 35% of all compounds are polymorphic."); *see also* J.A. 57373 ("The first step in the polymorph decision tree is . . . to attempt to answer the question: Are polymorphs possible?").

The Byrn article presents a flow chart that outlines a number of variables that may be adjusted during the recrystallization process to determine whether polymorphism occurs in a compound. Figure 1 below is the polymorphs tree presented in Byrn.

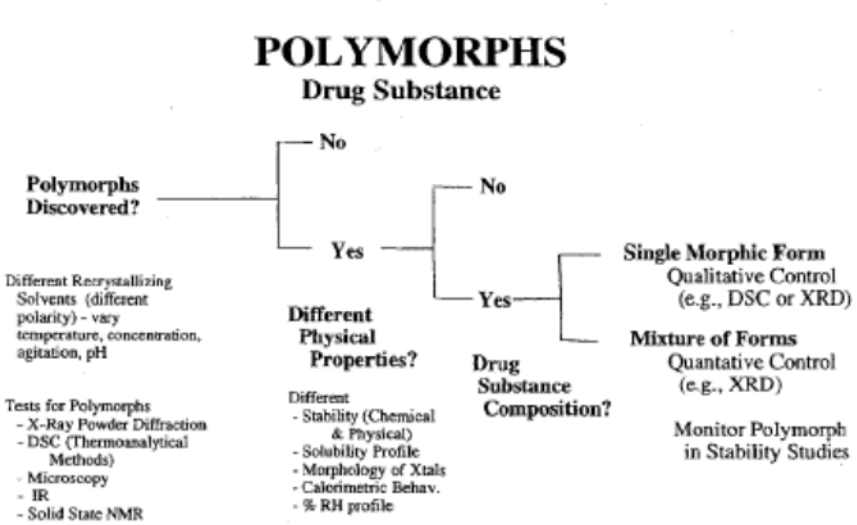


Figure 1. Flow chart/decision tree for polymorphs.

J.A. 57373. At the outset, Byrn lists a number of solvents to be used to recrystallize a substance to first determine whether polymorphs are possible. "Solvents should include those used in the final recrystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate." *Id.* Byrn does not disclose when it would be appropriate to use particular solvents or a particular mixture of solvents for recrystallization.

Byrn also instructs a POSA to "vary temperature, concentration, agitation, pH." *Id.*, Figure 1. Dr. Bernstein, Cross-Appellants' expert, testified that when it comes to solution recrystallization "there's a huge variety of solvents with temperatures, whether you stir or not, and . . . the crystallization is generally carried out by cooling. So the cooling rate can be a major factor in determining what you get." J.A. 10489–90 (142:24–143:3). But Byrn does not provide guidelines regarding which temperature, concentration, agitation, or pH levels are likely to result in polymorphs of particular compounds. It only notes that

these parameters should be varied. This lack of disclosure supports Dr. Bernstein's testimony that a POSA would have to manipulate the variables to "determine what the crystal form landscape looks like" because "you don't know what the result's going to be." J.A. 10493 (146:11–24). Indeed, a POSA could alter any number of variables and still fail to find a polymorph of a particular compound. J.A. 10494 (147:20–25); J.A. 8528 (228:15–21) (noting that polymorph investigations require varying parameters like temperature and solvents to "extend as broad as possible [the] range of investigations."); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007) ("To be sure, 'to have a reasonable expectation of success, one must be motivated to do more than merely 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.'" (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006)). Consequently, we hold that the district court did not clearly err in crediting Dr. Bernstein's testimony or concluding that Byrn provides insufficient guidance in discussing the wide array of conditions that could affect recrystallization, and therefore, the crystal structure of a resulting compound. *See Depomed Litigation*, 2016 WL 7163647, at *52–53.

Despite the lack of disclosure in Byrn, Alkem argues that any polymorph screening of a sample of tapentadol hydrochloride would result in Form A, either in whole or in part, because Form A is more stable at room temperature. Alkem contends that it is "not disputed" that the synthesis described in Example 25 of the '737 patent resulted in at least some Form A. Alkem Br. 34. In other words, Alkem asserts a POSA would have likely performed polymorph screening on a sample with some Form A if following the synthesis steps of Example 25. The record, however, does not support Alkem's argument.

Alkem advanced this same argument before the district court to allege that the '737 patent inherently anticipates the '364 patent, an issue that is not before us. The district court rejected Alkem's inherent anticipation theory because the method of synthesis that Alkem used, for purposes of this litigation, to produce a sample of tapentadol hydrochloride that comprised a mixture of Form A and Form B was not performed in accordance with the three steps outlined in Example 25 of the '737 patent. *Depomed Litigation*, 2016 WL 7163647, at *45–50. Instead, the mixture of Form A and Form B that Alkem relied on at trial was a result of performing only one of the three steps described in Example 25, whereas testimony showed that fully performing each of the three steps outlined in Example 25 results in only Form B. *Id.* at *46, *48, *50; *see also* J.A. 8557–60 (257:10–260:3) (stating resynthesis of Example 25 resulted in Form B); J.A. 8561 (261:11–19) (Example 25 resynthesis resulted in Form B and no Form A); J.A. 10497–10503 (150:20–156:21) (stating faithful reproductions of Example 25 result in only Form B, not Form A); J.A. 9729–30 (7:16–8:18) (same). Given the weight of evidence, we do not believe the district court clearly erred in concluding that Alkem failed to prove that synthesizing tapentadol hydrochloride according to Example 25 of the '737 patent resulted in only Form B. In addition, a POSA would not reasonably expect any polymorph screening of Form B to necessarily result in the "most stable form" of tapentadol hydrochloride (Form A, as Alkem argues). *See* J.A. 9773 (51:6–14) (stating there is no way to predict the most stable form without testing). Because the record indicates that there was (1) no known or expected polymorphism of tapentadol; (2) no evidence that the synthesis of Example 25 results in any Form A; and (3) no guidance as to what particular solvents, temperatures, agitation rates, etc., were likely to result in Form A, Alkem failed to prove that a POSA would have reasonably expected a polymorph screening of the Form B disclosed in the '737 patent to result in Form A.

Alkem also argues that the district court applied the wrong legal standard in its obviousness inquiry, requiring "absolute predictability," as opposed to a reasonable expectation of success. Indeed, in each of the cases Alkem cites, we did not require "absolute predictability," but acknowledged that the combination of prior art disclosures resulted in a predictable outcome. *See Pfizer*, 480 F.3d at 1364; *AstraZeneca LP v. Breath Ltd.*, 603 F. App'x 999, 1001–02 (Fed. Cir. 2015) ("*Breath*"); *see also Cubist Pharm., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1128–29 (Fed. Cir. 2015). However, each of these cases is inapposite to the facts at hand.

For example, in *Pfizer, Inc. v. Apotex, Inc.*, we determined that a POSA would have had a reasonable expectation of success to make amlodipine besylate based on the disclosure of amlodipine and a list of "53 FDA-approved, commercially marketed anions." 480 F.3d at 1355, 1361–69. Under the "particularized facts of [*Pfizer*]," such expectation was reasonable because a POSA would have narrowed the list of 53 anions "to a few" due to *known* characteristics of the anions. *Id.* at 1363, 1366–67. In other words, it was reasonable to expect that the combination of amlodipine and benzene sulphonate—one of the 53 anions disclosed the prior art—would likely result in amlodipine besylate because of the known acid strength, solubility, and other chemical characteristics of the benzene sulphonate. *Id.* at 1363.

In *AstraZeneca LP v. Breath Ltd.*, we concluded that a POSA would have had a reasonable expectation of success of producing the claimed sterile budesonide composition using known sterilization techniques even if the level of purity resulting from the methods was not actually known. 603 F. App'x at 1001–02. We did not require "actual success" in creating the claimed invention because the record abundantly supported the conclusion that four out of five known sterilization techniques would result in a sterile

budesonide product that met the purity limitations of the claims. *Id.* at 1002.

In *Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, we agreed with the district court's determination that it would have been obvious to use well-known purification techniques to produce a daptomycin-related substance having the recited purity levels. 805 F.3d at 1127, 1129. The asserted purity claims in *Cubist* recited each of the purification techniques that were described in the prior art. *Id.* at 1127–29. Using these purification techniques, the purity levels disclosed in each of these claims could be achieved. *Id.* at 1128 ("The purity patents do not point to any additional techniques that are necessary to obtain the recited purity levels in each of the claims."). Therefore, we concluded a POSA would have had a reasonable expectation of success in achieving the claimed purity levels because the purification techniques claimed in the patents used to achieve said purity levels were already known in the art. *Id.* at 1129.

The prior art processes described in *Breath* and *Cubist* were each known to purify substances, and therefore it was reasonably predictable that these methods would result in purity levels described in the claims. In *Pfizer*, the realm of possible anions could be reduced to a manageable number based on *known* properties of the anions, thus providing a POSA with a reasonable expectation of success. Here, a POSA did not know, or have reason to know, that tapentadol hydrochloride is polymorphic. Nor could a POSA know, or have reason to know, how the multiple variables involved in conducting a polymorph screen would affect the recrystallization of tapentadol hydrochloride. Byrn does not provide any guidance as to how the different solvents, varying temperatures, rates of agitation, or other variables used in polymorph screenings should be manipulated to even determine whether polymorphism occurs. *Cf. KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) ("If a person of ordinary skill can implement a predictable variation,

§ 103 likely bars its patentability."); *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (noting "predictability is a touchstone of obviousness"). This lack of knowledge in the field shows there was little to no basis from which a POSA could expect a probability of success in producing Form A.

Our decision today does not rule out the possibility that polymorph patents could be found obvious. But on the record here, the district court did not clearly err in finding a failure to prove that a POSA would have had a reasonable expectation of success at arriving at the claimed invention based on the prior art. As a result, we hold the district court did not commit legal error in concluding the '364 patent is not invalid as obvious.

Obvious to Try

Alkem contends that because Byrn discloses a finite number of solvents to use for recrystallization, it would have been obvious to try to produce Form A of tapentadol hydrochloride. To prove obviousness under an obvious to try theory, Alkem must show (1) a design or market need to solve a particular problem, *and* (2) that "there are a finite number of identified, predictable solutions" that would lead to an expectation of success. *KSR*, 550 U.S. at 421 (emphasis added).

As stated above, the district court did not clearly err in finding that Byrn identified many variables for screening, i.e., a "huge number of possible choices," as opposed to a "finite number," as contemplated in *KSR*. *See Depomed Litigation*, 2016 WL 7163647, at *53; *see also KSR*, 550 U.S. at 421. Rather, Byrn simply provides "a general approach" to polymorph screening, only giving "general guidance," without providing "detailed enabling methodology." *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 902–03 (Fed. Cir. 1988)). This court has explained that a conclusion of obviousness does not follow from merely "vary[ing] all parameters or

try[ing] 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." *Id.* at 1359 (quoting *O'Farrell*, 853 F.2d at 903). As already explained, the district court did not clearly err in finding that a POSA would not have had a reasonable expectation of producing Form A using the disclosure of the '737 patent and Byrn. Therefore, for the reasons stated above, it would not have been obvious to try to produce Form A based on the prior art in the record.

C. Utility

We now turn to the question of the '364 patent's utility. Utility is a question of fact. *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180 (Fed. Cir. 1991); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956 (Fed. Cir. 1983). The bar for utility is not high. *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). Nonetheless, a patent must have specific and substantial utility. *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) (citing *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563 (Fed. Cir. 1996)). The substantial requirement, also known as "practical utility," is satisfied when "the claimed invention has a significant and presently available benefit to the public." *Id.* To satisfy the specific prong of utility, the claimed invention must show that it can "provide a well-defined and particular benefit to the public." *Id.* In other words, a patent has utility if the alleged invention is capable of providing some identifiable benefit presently available to the public. *Id.* A patent fails to satisfy the utility requirement under 35 U.S.C. § 101 only if the invention is "totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992). For pharmaceutical patents, practical utility may be shown by evidence of "any pharmacological activity." *Fujikawa*, 93 F.3d at 1564.

Hikma contends that the '364 patent lacks specific utility because the specification vaguely states that "Crystalline Form A . . . has the same pharmacological activity as Form B but is more stable under ambient conditions. It can be advantageously used as [an] active ingredient in pharmaceutical compositions." '364 patent, col. 4 ll. 13–16. Hikma argues this disclosure fails to provide a "well-defined and particular benefit to the public." Hikma Br. 32 (citing *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005)).

Hikma's arguments are without merit. The '364 patent teaches that "[t]he crystalline Form A according to the invention is used for the treatment of pain or the treatment of urinary incontinence." '364 patent, col. 4 ll. 63–65; *see also id.*, Abstract. The prior art confirms that tapentadol hydrochloride was known as an analgesic at the time of filing of the '364 patent, as does the expert testimony given at trial. *E.g.*, J.A. 58128; J.A. 9843 (121:15–17); J.A. 10898 (21:3–17). Therefore, the '364 patent concretely discloses the practical benefit of Form A of tapentadol hydrochloride as an analgesic.

Hikma next argues that to show substantial utility, Form A's superior stability over Form B at room temperature must not only be proven, but must be proven by test data. Hikma attempts to set too high a bar for purposes of finding a sufficient disclosure of utility. While test results often support claims of utility in patents concerning pharmacological arts, such testing is not always required. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) ("[I]t is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct." (quoting *In re Jolles*, 628 F.2d 1322, 1325 (CCPA 1980)). Nor do said results need to prove the claimed utility. *E.g.*, *Fujikawa*, 93 F.3d at 1564 ("[T]est results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be *reasonably* indicative of the desired [pharmacological] response."

(internal quotations and citations omitted)). All that is necessary is evidence that a POSA would accept the claimed utility as correct.

The district court found that a POSA would have believed that, at the time of filing the '364 patent, Form A was more stable than Form B at room temperature, i.e., "ambient conditions." Example 16 describes a variable temperature XRPD experiment that produced Form B from Form A at temperatures (40–50° C) higher than room temperature. '364 patent, col. 18 ll. 53–57. This effect is "reversible with Form B changing over into Form A at lower temperature." *Id.* col. 18 ll. 56–57. Expert testimony confirmed the results of Example 16, namely that Form A is stable at room temperature and Form B is stable above 50° C. J.A. 10471–72 (124:9–125:6); *see also* J.A. 9694–96 (57:14–59:7); J.A. 9800–02 (78:25–80:20). There is sufficient proof that the disclosure of Example 16 is reasonably indicative of the stability of Form A at room temperature. There is also sufficient evidence that thermodynamic stability is considered beneficial for purposes of storage and consistency in manufacturing, which can be beneficial characteristics for pharmaceutical compositions. J.A. 9107 (86:18–23), J.A. 9798 (76:9–12). Cross-appellants need not prove that Form A has superior stability over Form B for purposes of determining utility. *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."). It is sufficient that Form A is shown to be stable at room temperature and useful for pain relief.

For these reasons, we hold that the district court's finding of utility was not clearly erroneous.

Hikma makes additional arguments regarding the validity of the '130 patent to be considered only if this court reverses the district court's findings of noninfringement of

the '130 patent. Because we affirm the findings of noninfringement, we need not reach these issues.

CONCLUSION

For the foregoing reasons, we affirm the judgment of the district court.

AFFIRMED

COSTS

No costs.