No. 2017-1153, -2048, -2049, -2050

In the
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.

Appeal from the United States District Court for the District of New Jersey,
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, and 2:15-cv-06797-CCC-MF.
The Honorable **Claire C. Cecchi**, Judge Presiding.

ALKEM LABORATORIES' RESPONSE AND REPLY BRIEF

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CERTIFICATE OF INTEREST

I, Imron T. Aly, Counsel for Defendant-Appellant Alkem Laboratories Limited, certify the following:

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

Alkem Laboratories Limited

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Alkem Laboratories Limited, as named in the caption, is the real party in interest.

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

Alkem Laboratories Limited has no parent corporation and no publicly traded company owns more than 10 percent or more of its stock.

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 are:

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5. There are no cases 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.

Dated: January 31, 2018

Respectfully submitted,

/s/ Imron T. Aly
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SUMMARY OF THE ARGUMENT

The polymorph patent claims 1-3 and 25 of the '364 patent are obvious, and the district court committed legal error by requiring absolute predictability to conclude otherwise. The proper legal standard was met by showing that the claimed invention would have been the result of a routine polymorph screen, not that the exact dimensions of the resulting crystal structure could have been predicted before the screen was done. Alkem showed that the alleged invention would have resulted from the established prior art protocol for polymorph screening—including evidence that the published routine screen resulted in Form A tapentadol—so the asserted claims should have been found obvious. Grünenthal does not deserve patent exclusivity for claiming the results of the same routine screen that any person of ordinary skill in the art would have done.

Grünenthal's opposition brief raises factual issues that have nothing to do with the question presented. The question presented is whether predictability of the result was required ahead of time, or if it was enough to show that the result was based on a routine prior art screen. Grünenthal, however, addresses other issues that do not affect that question. For example, even though Grünenthal recognizes that Alkem did not appeal the district court's finding on anticipation (Resp. Br. at 15-16), Grünenthal still argues that the prior art did not anticipate. (*Id*. at 19-20.) As another example, Grünenthal explains how it worked really hard to develop the tapentadol

molecule (*id.* at 5-6), but that has nothing to do with whether the later polymorph was obvious. Grünenthal similarly discusses at length the internal work that it did to explore polymorphs, but that has nothing to do with obviousness, which is based on published literature and the outsourced routine polymorph screen done by third party SSCI. It is not surprising that Grünenthal itself was not very efficient: even though polymorph screening was a well-established field, Grünenthal had no internal experience with polymorphs until tapentadol. (*Id*. at 6-7.)

The asserted polymorph claims are obvious because they added nothing to the prior art: the claims represent the resulting dimensions for a polymorph that anyone would have obtained by doing a routine prior art screen. This is even more so the case here, because tapentadol only exists in two polymorph forms: Form A and Form B and, of those two, Form A is the one stable at room temperature. (Appx66; Appx146-147.) The asserted claims are at least obvious to try, because the prior art already explained how to do a prior art polymorph screen, with a finite number of solvents, and the routine screen would inevitably show and did show the easily-available polymorphs. If this decision is not reversed, then no polymorph patent can ever be obvious if it claims the specific dimensions of the resulting crystal structure—even after following the established and routine polymorph screen.

ARGUMENT

I. The District Court Committed Legal Error By Requiring Absolute Predictability For The Dimensions Of A Polymorph Resulting From A Routine Screen

In finding that "the determination of the structure and properties of the polymorph forms of tapentadol hydrochloride would have been impossible to predict," the district court considered the wrong legal test. (Appx143-144.) Under that test, patents will be conferred on the most routine applications of prior art polymorph screens to existing compounds, only because the specific results were claimed and those results were not "predictable." The appropriate legal question was not whether the "structure and properties" of polymorph forms were predictable, but rather whether they were the result of a routine polymorph screen that any person of ordinary skill in the art would have done.

A. The District Court's Analysis Relied Upon Absolute Predictability

The district court erred by using predictability as the requirement, when only a reasonable expectation of success was required. "Obviousness does not require absolute predictability of success," but rather "a reasonable expectation of success." *Medichem, S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988).) The proper legal standard for obviousness is whether a person of skill in the art would have been motivated to follow the prior art combination and that the skilled artisan would have had a ***reasonable expectation of success*** from doing so. *See Bristol-Myers Squibb Co. v.*

Teva Pharm. USA, Inc., 752 F.3d 967, 973 (Fed. Cir. 2014); *Pfizer Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007); *Velander v. Garner*, 348 F.3d 1359, 1363 (Fed. Cir. 2003). As Alkem explained in its Opening Brief, the district court did state the correct standard in the legal background section, but did not use that standard in connection with its polymorph analysis. (Alkem Br. 22-23.)

The district court erroneously applied an absolute predictability standard, stating that the "results of the polymorph screen…would have been impossible to predict." (Appx143-144.) The district court similarly stated that polymorphic screening consists of "unpredictable application of [] routine techniques," relying again on the unpredictability of the resulting polymorph structure itself. (Appx143, Appx57384, Appx10921-10922 at 44:5-45:12, Appx10789-10791 at 213:20-215:8, Appx10794 at 218:20-24, Appx10795-10797 at 219:21-221:11.) As noted in Alkem's Opening Brief, absolute predictability is not required, a theme repeatedly addressed by this Court. *See, e.g.*, Alkem Br. at 22-28 (discussing *Pfizer*, *AstraZeneca*, *Cubist*, and *Santarus* decisions). In each of those decisions, the patent owner argued that the claimed properties were not *a priori* predictable, but each time this Court concluded that predictability was not the proper standard for obviousness.

B. Grünenthal Acknowledges That Predictability Was Not The Right Test, But Relies Upon It Anyway For Its Argument

Grünenthal at first does not seem to dispute that it is wrong to require absolute predictability. In its brief, Grünenthal distances itself from its own expert Dr.

Bernstein—who had testified predictability is required—and states that "[c]learly, Dr. Bernstein has not applied and was not applying the legal principles of obviousness to every possible polymorph." (Resp. Br. at 50; Appx11043-11044 at 30:23-31:2.) Grünenthal even plainly states that its position is ***not*** that "one must have the ability to 'absolutely' predict the number of polymorphic forms that tapentadol hydrochloride would have or their respective stabilities." (Resp. Br. at 32.)

Despite its acknowledgment that requiring absolute predictability was improper, Grünenthal still argues that "predictability is a critical factor in the obviousness analysis." (*Id*. at 45.) Grünenthal requires predictability of the result and argues that disclosures did not already exist in the prior art "on the particular form of the invention (Form A of tapentadol hydrochloride) or how to achieve it" (*id*. at 48), and that "nothing whatsoever was known about the crystalline landscape of tapentadol hydrochloride." (*Id*. at 49.) Grünenthal even argues that the district court's statement "predictability is a touchstone of obviousness" is excusable because it was quoting from *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). (Resp. Br. at 46.) But *DePuy* only helps Alkem's argument, because the district court's quote from that case was taken out of context from the rest of the sentence, which makes clear that "predictability" in *KSR* does not require predicting the resulting properties from an obvious

combination: "Although predictability is a touchstone of obviousness, the 'predictable result' discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose." *DePuy Spine, Inc.*, 567 F.3d 1326.

As discussed in detail in the next section, the combination of the Byrn polymorph screen and tapentadol made the invention obvious. These two prior art components were not only capable of being combined but were expected to work for their intended purpose of identifying easy-to-find polymorphs. That conclusion is supported by the district court's factual findings that confirmed "[a] POSA would have understood as of June 2004 how to conduct a polymorph screen and there were publications that provided guidance on how to do such a screen." (Appx140.) That is all that was required: in *Pfizer*, this Court ruled that even where it is "unpredictable as to whether a particular salt would form and what its exact properties would be," that is not the required test and only "a reasonable (although not guaranteed) expectation" is enough. 480 F.3d at 1364, 1366. To hold otherwise would yield "a rule of law equating unpredictability to patentability" such that "any new salt—including those specifically listed in the [prior art]—would be separately patentable." *Id*. at 1364. Here, the Byrn article provided the expectation that it would yield at least the readily-available polymorphs "in the majority of cases." (Appx57372-57381 at 57372). Even where there are many variables that "require

extensive time, money, and effort," inventions are still obvious where they involve only "routine" steps to a POSA. *Id*. at 1367-68.

Grünenthal's response to the Federal Circuit precedent is to dismiss it in conclusory fashion, offering a sentence for each case. For example, Alkem showed that *Santarus, Inc. v. Par Pharms., Inc.* addressed a similar situation, where the claimed properties were not predictable but the invention itself was obvious. 694 F.3d 1344 (Fed. Cir. 2012); (Alkem Br. at 35.) The Court found "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." *Santarus*, 694 F.3d at 1354. Grünenthal attempts to distinguish *Santarus* with this sentence: "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." (Resp. Br. at 52.) Grünenthal's argument is conclusory and circular, because it requires Form A to have already been in the prior art (which would have been anticipation), when the argument is based on obviousness. The argument also ignores the district court's factual finding that Grünenthal's own witnesses conceded "that polymorph screening was a common technique that involved using different common solvents and temperatures to test for polymorphs." (Appx140.) The prior art already disclosed tapentadol and how to make routine polymorphs, so reframing

that obvious combination by simply claiming the resulting properties does not make the polymorph patentable.

II. The '737 Patent Combined With The Byrn Reference Rendered Obvious The Asserted Claims

The '737 patent disclosed tapentadol and its pharmaceutical use, Byrn disclosed how to search for polymorphs, and the FDA Guidance (and also discussed in Byrn) provided express motivation to combine the two. As discussed above, the question is not whether the specific claimed dimensions were predictable ahead of time, but whether a POSA would expect that using the established polymorph screen would yield readily-available polymorphs. As did the district court, Grünenthal erroneously relies upon a lead compound analysis for selecting tapentadol, rejects the significance of the Byrn reference, and argues that obviousness is based on hindsight. Each of these arguments is addressed in this section.

A. The District Court Committed Legal Error In Applying A "Lead Compound" Analysis

In response to Alkem's argument that the district court essentially required a lead compound analysis (Alkem Br. at 31-32), Grünenthal states that the district court "did not require Alkem to prove a 'lead compound' analysis" but that "it would not be improper to do so." (Resp. Br. at 39.) Though the district court did not use the phrase "lead compound," it did require something "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.) That is the lead compound analysis, and it was legal error to apply it here.

The lead compound analysis is limited to new chemical compounds, not properties of existing compounds. *See Otsuka Pharm. Co. v. Sandoz Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012) (holding that lead compound analysis is applicable where patentability of a new chemical compound is at issue); *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009) (same); *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) (same). Grünenthal's reliance on *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) repeats the same legal error: that too was a new compound case. (Resp. Br. at 27.) So are many of the other cases that Grünenthal cites, such as on pages 26-28 of its brief. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 995-97 (Fed. Cir. 2009); *Pfizer Inc. v. Teva Pharm. USA, Inc.* 555, Fed. Appx. 961, 969 (Fed. Cir. 2014).

A polymorph is not a new compound. Instead, a polymorph results from the different ways in which molecules of a single compound are arranged in space. Polymorphism is "the ability of a chemical compound to crystallize in more than one crystal structure." (Appx44.) We have not identified a polymorph case where the lead compound analysis was applied, nor does Grünenthal cite to any such case.

Thus, there was no reason to require picking out a particular compound from the '737 patent. This case is analogous to *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, where this Court found that an enantiomer of a prior art compound was obvious because the claimed invention was the result of applying known techniques (there, separation) to a previously disclosed compound (there, Example 20). 499 F.3d 1293, 1302 (Fed. Cir. 2007).

Aventis went on to hold that "in the chemical arts […] 'structural similarity between claimed and prior art subject matter…where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness.'" *Id.*, (quoting *Takeda*, 492 F.3d at 1356.) Obviousness can therefore be met by showing the close relationship of "structural similarity," and in this case there is identity in the chemical formula of two polymorphs, and the two crystal forms are almost identical too. (See Alkem Br. at 43.) In fact, in response to the utility argument on appeal, Grünenthal goes out of its way to explain that "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." (Resp. Br. at 55.)

B. Even If A Lead Compound Analysis Was Appropriate, The District Court Erroneously Determined That A POSA Would Not Have Selected Tapentadol

Even if there had been a requirement to identify tapentadol in particular, then the district court clearly erred by finding "there is nothing in particular in the '737

patent that would have motivated a POSA studying crystal structure to select tapentadol." (Appx142.) The '737 prior art patent reported that the "compounds of formula I," which include tapentadol, "are suitable as pharmaceutical active ingredients in drugs" and "preferably used for the treatment of pain." (Appx377 at 5:41-47.) That patent identified 28 example compounds, and of those, only one was separately identified in a pharmaceutical product update published by the World Health Organization. (Appx10191-10192 at 144:1-145:21.) The district court did not even mention this fact, which was important because the 2002 WHO listing identified tapentadol hydrochloride in particular as a pharmaceutical product for pain relief, an "analgesic." (Appx58128.) Dr. Steed further testified that Example 25 of the '737 patent confirmed tapentadol "can be made in crystalline form" and that "a person of skill [would] be motivated to find out if there was more than one crystal structure." (Appx9714 at 77:3-10.)

If anything more was required to suggest to a POSA that tapentadol was a useful compound from the compounds identified in the '737 patent, then the patent fails the utility requirement of 35 U.S.C. § 101 and the reissue-original patent rule. As explained in the Opening Brief, the district court found that the '593 patent—which has the same specification as the '737 patent—identified tapentadol hydrochloride in particular as a useful compound. (Alkem Br. at 32.) Indeed, addressing the original patent rule, the court found that the '593 patent "clearly and

unequivocally disclose[d] the newly claimed invention [tapentadol hydrochloride] as a separate invention." *Antares Pharma, Inc. v. Medac Pharma Inc.*, 771 F.3d 1354, 1362 (Fed. Cir. 2014); (Appx91, Appx124.) Moreover, also according to the district court, "a POSA would have had a reasonable expectation that Example 25 (tapentadol hydrochloride) would have a dose-dependent antinociceptive effect due to its structural similarity to the family of compounds that demonstrated analgesic activity." (Appx119.) Notably, Grünenthal does not address the district court's findings showing that tapentadol hydrochloride was adequately singled out.

C. The Byrn Reference Disclosed How To Do A Routine Polymorph Screen, Which Would Have Resulted In Form A Tapentadol

Following the prior art routine screen, as applied to tapentadol, results in the Form A polymorph. This is not a case where some of the published first-pass screen techniques resulted in Form A, while others resulted in Form B (the only two forms of tapentadol that exist). Instead, all of them resulted in at least some Form A, which is all that the claims require; there is no purity threshold in any of the asserted claims. SSCI is a third party company that offered standard polymorph screens, and did so for Grünenthal as well. SSCI followed the evaporation crystallization protocol disclosed in the Byrn article and used the solvents listed in the Byrn article. (Appx49380-49567 at 49393-49394; Appx57372-57381 at 57373.) And in just three weeks, and no matter what solvent SSCI used in its screens, any time crystalline material was formed, some Form A was present. (Appx49380-49567 at Appx49388,

Appx49393-49395, Appx9718-9719 at 81:13-82:14, Appx11043 at 30:6-10.) Those solvents include each of the solvents from the Byrn article to use with a polymorph screen. In doing what anyone in the prior art would have done, SSCI proved that a POSA would have found Form A.

In response, Grünenthal argues that it is "vigorously disputed" that the '737 protocol for making tapentadol hydrochloride resulted in either Form A or B. (Resp. Br. at 16.) But it is not clear how Grünenthal can make that argument, because Grünenthal itself argued these were the only two alternatives. (Appx17736.) Grünenthal now states that the '737 protocol would result only in Form B. (Resp. Br. at 16-18, 32.) It said the opposite during litigation, when it was asked about the basis for language in the '364 patent. The '364 patent contains several examples, each of which state that the starting material was "prepared according to example 25," referring to the same example 25 as in the '737 patent. (Appx399 at 5:16-18, 39-42, 57-59; 6:9-11, 30-33; Appx400 at 7:35-37.) In its discovery responses, when asked what samples were used for the '364 patent examples, Grünenthal pointed to an SSCI report reflecting work that SSCI had done for a polymorph screen. (Appx48962-48976 at 48968-48971.) That report, in turn, confirmed that the starting material "prepared according to example 25" was Form A tapentadol. (Appx49380-49567 at 49384, 49392.) The district court recognized that Grünenthal made that admission that example 25 could result in Form A, but found that it did

not mean that the '737 procedure always resulted in Form A. (Appx136.) So when Grünenthal now claims "faithful reproduction of Example 25 yields only Form B," (Res. Br. at 16), that contradicts its own admissions in the litigation.

In any event, Alkem is not relying on the '737 patent by itself for invalidity, so the particular crystal form from Example 25 does not matter. The obviousness combination is instead the '737 patent in combination with the routine polymorph screen disclosed in the Byrn reference. As to that combination, and regardless of what Example 25 yields, using the solvents in the Byrn reference always resulted in at least some Form A. Moreover, only Form A is stable at room temperature (Appx146-147), so it would be difficult to avoid it in any screen, further explaining just why Form A was so ubiquitous.

1. The SSCI Testing Confirms What A POSA Would Find Using The Byrn Prior Art Protocol

Byrn expressly taught that "[t]he first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question: *Are polymorphs possible*." (Appx57373.) The article provided guidance about how to do that, with instructions for a routine polymorph screen. It set forth crystallization techniques, and solvents to use. (*Id.*) Therefore, a POSA would have a reasonable expectation of success that following the established Byrn protocol to screen for polymorphs would reveal those polymorphs that were easily and routinely available. Byrn itself reports that applying "basic

physicochemical principles combined with appropriate analytical methodology can provide a strategy for scientific and regulatory decisions related to solid state behavior in the majority of cases." (Appx57372-57381 at 57372.)

In this case, what the Byrn screen would have showed to a POSA for tapentadol is not based on theory or litigation-inspired testing. To the contrary, Grünenthal itself outsourced the tapentadol polymorph screen to SSCI, a third party. In fact, the person who founded SSCI was the very same Dr. Byrn who authored the Byrn reference at issue. (Appx11036 at 23:6-10.) The SSCI screen results provide independent confirmation that following the prior art screen would result in Form A. After all, it is not as if Byrn or anyone else at SSCI was named as an inventor, nor could they have been. They only did a routine screen, following their own published prior art protocol.

2. Conditions Did Not Need To Be Further Specified, As A POSA Could Do A Polymorph Screen

Grünenthal again refers to predictability, stating that polymorph screening can "include[] a large variety of conditions" such that "the results of the polymorphs screen … would have been impossible to predict." (Resp. Br. at 26-27 citing Appx143-144.) Predictability is the wrong test, and the Byrn article provided adequate detail for a POSA to do a routine screen. That was the entire point of the article, in order to direct those developing pharmaceutical products to satisfy the FDA's guidance to do a polymorph screen. It was well within a POSA's knowledge

to address the variables that the district court identified, which were "temperature, stirring, cooling rate, seeding, and whether an anti-solvent is used." (Appx143.) By analogy, though a prior art cake recipe may not specify mixing time or icing instructions, an experienced baker is well aware of standard variables and conditions. The same is true here. The mundane detail that the district court and Grünenthal seem to require flies in the face of a POSA's knowledge, who is expected to know how to implement what Dr. Bernstein wrote were "traditional" protocols. (Appx59463-59481 at 59465-59466.) In his underlying publication, Dr. Bernstein distinguished that "traditional" solvent approach with other techniques, which were newer and used more rarely. (*Id.* at 59466.) As this Court has explained, "routine" experimentation that may require "time and care" does not make a claimed invention nonobvious. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989). Grünenthal never disputed that the Byrn reference was enabled. Indeed, the district court found and all experts agreed that a POSA knew how to conduct a routine polymorph screen. (Appx139-140; Appx9715-9716 at 78:20-79:23; *see also* Appx11023 at 10:11-21.) As Dr. Steed testified at trial, and it was not opposed, the process for doing a polymorph screen—including of the variables and conditions one could use—is still "really quite straightforward." (Appx9783 at 61:5-7.)

The district court's finding about how there can be different variables therefore used the wrong legal standard and was factually clearly erroneous. For the

legal standard, the district court referred to general variables and not the prior art combination that Alkem presented. Alkem's combination was not based on the general knowledge of a POSA combined with tapentadol hydrochloride. Rather, the obviousness combination specifically combined the Byrn reference with tapentadol hydrochloride. That distinction makes a difference because the Byrn article outlined the specific protocols to be pursued, and explained that "[t]he first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents"—and listed the nine solvents to use for that first step. (Appx57372-57381 at 57373.) Moreover, the Byrn article is important because SSCI followed the published protocol and tested those same solvents, confirming what a POSA would have done applying the Byrn article. (Appx49380-49567 at 49393-49394; Appx57372-57381 at 57373.) Despite the number of variables one can imagine now, the "first step" was to simply crystallize the substance in different solvents that Byrn specifically listed, and that was in and of itself enough to obtain Form A tapentadol. The fact that Grünenthal outsourced the polymorph screen to SSCI confirms that identifying Form A was not inventive, but the routine and mechanistic application of the prior art screen.

In addition, it is irrelevant if different conditions could have a different result, so long as the claimed combination and conditions were obvious and within a POSA's skill. Like with the 53 salts in *Pfizer v. Apotex*, one could envision various

reaction conditions and not know which would work best or what the results would be, but so long as the reactions themselves are routine then the case is "analogous to the optimization of a range or other variable within the claims." 480 F.3d 1348 at 1368 (Fed. Cir. 2007). The same is true here, and although one could envision various conditions for how to do a crystallization reaction, there is no requirement to predict ahead of time which will work best. Moreover, the district court already found that "[a] POSA would have understood as of June 2004 how to conduct a polymorph screen and there were publications that provided guidance on how to do such a screen." (Appx139-140.) And unlike the 53 different anions disclosed in the prior art in *Pfizer*, Byrn disclosed only nine: "solvents should include those used in the final crystallization 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." (Appx57372-57381 at 57373.)

In fact, not only did the prior art in this case list only nine solvents (*id*.), but all of them resulted in Form A. (Appx49380-49567 at 49393-49394). In *Pfizer*, it was not clear whether all 53 salts worked or not, but the invention was still obvious given the reasonable number of first-choice options. It was legally erroneous to rely on general unpredictability to overcome obviousness. As in *Allergan, Inc. v. Sandoz Inc.*, "the district court erred in finding that there was no reasonable expectation of

success in view of the general unpredictability of the formulation arts." 726 F.3d 1286, 1292-93 (Fed. Cir. 2013); *see also Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 730 (Fed. Cir. 2017) (affirming invalidity even though variables – like addition of base, temperature range, and moisture content – were not expressly disclosed in the prior art).

3. The SSCI Testing Results Reveal Inherent Properties Of Form A Tapentadol

Grünenthal argues that Alkem relies on "hindsight" to explain that there are only two forms of tapentadol and that Form A is the stable form at room temperature. (Resp. Br. at 30-34.) Not so. These are inherent properties of the compound, and confirm that any POSA would have found the same Form A by following the Byrn protocol. In fact, Grünenthal concedes in response to the utility argument on appeal that "Form A 'is more stable under ambient conditions.'" (Resp. Br. at 56.)

The inherent properties of tapentadol hydrochloride and the results of SSCI's third party work are not hindsight evidence. "[S]o long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure," there is no impermissible hindsight. *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971). SSCI was not an inventor. It was a third party that followed a published protocol.

The ’737 patent already disclosed that tapentadol hydrochloride resulted in a crystal form, without specifying the details of what that form was, but still showing that it was amenable to a polymorph screen. (Appx63; Appx384 at 19:65; Appx9714 at 77:3-6.) Dr. Steed testified that Example 25 of the ’737 patent indicated that the material was crystalline, even if the exact crystal structure was not disclosed; that tapentadol “can be made in crystalline form;” and that “a person of skill [would] be motivated to find out if there was more than one crystal structure.” (Appx9714 at 77:3-10.) This expressly supported a reasonable expectation of success that a POSA would be able to determine the readily-available polymorphs.

Grünenthal hypothesizes that the ’737 patent teaching that tapentadol “crystallised out” of solution could refer to “a polymorph, solvate, hydrate, or a mixture of materials.” (Resp. Br. at 18.) The district court made no such finding. But even if so, the same Byrn reference would have resulted in finding readily-available polymorphs, because it addressed the FDA’s request to identify any of these solid forms: the FDA guideline asked that “‘appropriate’ analytical procedures should be used to detect polymorphic, hydrated, or amorphous forms of the drug substance.” (Appx57372-57381 at 57372.) Indeed, the explicit directive in the Byrn reference was to “provide a strategic approach to remove much of th[e] uncertainty” in complying with the FDA guidelines to use “appropriate analytical procedures […]

to detect polymorphic" forms of a compound. (*Id*.) The Byrn polymorph screen would have revealed any of the polymorphs, including Form A.

The state of the art for polymorphs was so established by 2004 that one could simply outsource it to SSCI, and the inherent properties of tapentadol made it inevitable that one would identify Form A. The SSCI report is evidence not relied upon as its own prior art, but to show that following the Byrn protocol would have resulted in Form A, based on what any POSA would have done. SSCI conducted a standard polymorph screen which merely followed the directions provided in the Byrn article. (*See* Alkem Br. at 33.) Indeed, both side's experts explained that polymorph screening was known and routine. (Appx9717-9719 at 80:4-82:14; *see also* Appx11023 at 10:11-16.) Even Grünenthal's expert conceded that such simple crystallization experiments—used in polymorph screens—are one of the first things chemists learn. (Appx11023 at 10:11-16, Appx59463-59481 at 59465.) The SSCI results prove what a POSA knew and would do, particularly in view of its consistency with the Byrn protocol. It is entirely appropriate to use unpublished materials to show "the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015); *see also Thomas & Betts Corp. v. Litton Sys., Inc.*, 720 F.2d 1572, 1580-81 (Fed. Cir. 1983) (recognizing patentee's internal documents "as indicators of the level of ordinary skill in the art").

In a further attempt to argue hindsight, Grünenthal mischaracterizes Alkem's argument when it states: "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 . . . ." (Resp. Br. at 32 (emphasis in original).) But Alkem's argument relies on neither premise. Instead, Alkem explained how testing confirmed two inherent properties about tapentadol, which even if unknown in the prior art, help to show why as a scientific reality any POSA would have found Form A. One property is that tapentadol has only two polymorphs, (Appx66), and even though that was not known before the testing was done, it helps to show that a POSA would have found Form A because it was not one of many possible polymorphs (where variable conditions may matter). Another inherent property is that Form A is the form that is stable at room temperature. (Appx146-147.) Grünenthal did not do anything to make it stable. Following the Byrn protocol makes it likely that any POSA would find Form A because it is room-temperature stable, whereas consistently creating a stable Form B was a challenge. (Alkem Br. at 14.) In fact, these are the same inherent properties that Grünenthal relies upon to argue that the asserted claims have utility. (Resp. Br. at 56-60.)

4. Grünenthal's Other Attempts To Avoid The SSCI Results Represent New Arguments, Which Are Also Contradicted By the Record

That Grünenthal allegedly provided Form A starting material to SSCI is irrelevant, as confirmed by Grünenthal's own expert testimony at trial. As a preliminary matter, this is a new argument that Grünenthal raises for the first time on appeal, about the starting material affecting SSCI's screen, so should not be considered. But even if it is considered, Grünenthal has already successfully argued the opposite and is estopped from changing its position now. In response to allegations of unclean hands, Grünenthal argued that there was "no evidence that the crystal form of the starting material for [Examples 7 or 25] would have had any impact whatsoever on the PTO's decision to grant the '364 patent." (Appx17813; Appx17971 at ¶697; Appx17924 at ¶¶489-91.) Grünenthal confirmed that even if it gave Form A to SSCI and reported it as Form B in the '364 patent, that was irrelevant because it could not have influenced the result. (Appx17970-17971 at ¶¶694, 697.) Grünenthal's expert, Dr. Bernstein, testified that when conducting polymorph screens the crystalline form that is used at the start is completely irrelevant, because the product goes into solution and then is ***re***-crystallized, which is what determines the resulting crystal form. He was adamant that "[i]t doesn't matter, really doesn't matter whether it's form A or it's form B. You are doing a recrystallization. So, you are going to dissolve the material. Once it dissolves, it doesn't matter which

form it was to begin with." (Appx10869 at 293:14-19.) Named inventor Dr. Gruss similarly testified that the starting material for polymorph purposes is "not of importance because you dissolve it afterwards." (Appx8899 at 59:9-14.) The district court accepted these arguments, and found for Grünenthal on the unclean hands issue, because "the first step of Example 2 was to dissolve the tapentadol hydrochloride in acetone, at which point the tapentadol hydrochloride in solution is no longer in crystalline form." (Appx152.) Even in its brief, Grünenthal still concedes in opposing the utility argument that "when tapentadol hydrochloride is dissolved, for example in the gastric fluid of the stomach, no crystal structure remains." (Resp. Br. at 55.) Grünenthal cannot shift its argument now.

In addition, Grünenthal is incorrect about whether the Byrn technique renders obvious the claimed invention, because Grünenthal's argument is focused only on the "slurry" results or the additional solvents on top of those in the Byrn reference. (Resp. Br. at 14-15.) Once again, this is a new argument raised on appeal, so should not be considered. And even if the argument is considered, a slurry experiment is only one kind of test that can be done. Grünenthal ignores the other types of polymorph screens including the well-established screen testing that SSCI did based on the Byrn reference solvents. Each of the non-slurry tests still resulted in at least some Form A, as did all the solvents published in the Byrn article. (Appx49380-49567 at 49393-43934.) No matter what solvent or conditions SSCI used in its

screens, any time crystalline material was formed, some Form A was present. (*Id.*; Appx9718-9719 at 81:13-82:14; Appx11043 at 30:6-10.)

As a last-ditch effort to avoid the SSCI results, Grünenthal theorizes that it must have provided something more to SSCI other than the tapentadol starting material. (Resp. Br. at 14.) This is a third new argument that Grünenthal did not raise below, so should not be considered. Even if it is considered, Grünenthal offers no evidence for this theory, because there is none. Its brief instead cites only to SSCI's documents – not Grünenthal's – including SSCI's screening protocol at Appx59457-59458[1] and the results from that protocol at Appx49393-49394, which of course do not show that Grünenthal provided SSCI with anything other than the initial tapentadol sample. (Appx49384.) Grünenthal does not say or show what it gave Grünenthal other than that sample, and the district court made no such finding either. In fact, Grünenthal's argument contradicts its own litigation admission. As confirmed at trial, Grünenthal provided only one sample to SSCI that was used for the routine screen that is reported in the SSCI test results. (Appx49380-49567 at 49384, 49392; Appx8902 at 62:9-15; Appx8903 at 63:9-12.)

[1] "*Copyright 2001- This protocol is the property of SSCI, Inc. Permission is required to use the ideas and procedures container herein*" appears at the bottom of every page of SSCI's Screening Protocol (Appx59453-59462).

D. Because Absolute Predictability Is Not Required, The Asserted Claims Are Obvious In View Of The '737 Patent And Byrn

Had it applied the legal standard correctly, the district court already made the factual findings to show obviousness. Grünenthal concedes that the district court determined 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." (Resp. Br. at 36 citing Appx139-140.) Indeed, the Byrn reference was published specifically in view of the FDA guidelines. The Byrn reference states that "[t]his review is intended to provide a strategic approach to remove much of this uncertainty." (Appx57372-57381 at 57372.) Byrn identified the steps for a routine screen, and Dr. Byrn's company, SSCI, performed that routine screen. The district court correctly concluded that "[a] POSA would have understood as of June 2004 how to conduct a polymorph screen." (Appx140.)

Alkem showed that a POSA would be motivated to combine the '737 patent with the Byrn reference, because of the established practice to screen polymorphs as part of any pharmaceutical product development and the express FDA guidance. The district court found that "Grünenthal generally understood that pharmaceutical companies take consideration of polymorphism when they are developing pharmaceutical compounds." (Appx140.) Moreover, there was express motivation

to combine the prior art because of the FDA guidance; the district court already found that "[a]s early as 1987, the FDA had issued guidelines indicating that '[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs." (Appx139.) That was enough to show obviousness, because a POSA knew how to do the published polymorph screen and had a reason to do so.

Just like applying routine isolation techniques to prior compounds renders the resulting enantiomer obvious, applying routine crystallization to prior compounds renders the resulting polymorph obvious. Again referring to the enantiomer example in *Aventis*, "[i]f it is known how to perform such an isolation, doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" 499 F.3d at 1302. Testing for polymorphs was so routine that it could be outsourced. Grünenthal's expert agreed that "[c]rystallization from solution is one of the first laboratory skills that chemists acquire, and applying variations to the conventional methods has been a traditional strategy in the search for polymorphs." (Appx59463-59481 at 59465.) The approach is just like the isolation techniques used for enantiomers, for which "isolation of interesting compounds is a mainstay of the chemist's art." *Aventis*, 499 F.3d at 1302.

1. Grünenthal's District Court Cases Do Not Support Its Position

Even though Federal Circuit authority including *Pfizer*, *AstraZeneca*, *Cubist*, *Santarus*, and *Aventis* all support the same proposition—that one cannot claim

unpredictable properties to overcome an obvious combination—Grünenthal refers to a series of district court cases that did not receive appellate review. Each of those would have presented a similar issue if appealed, that absolute predictability of particular properties is not required in order to show obviousness. The other district court decisions are not, however, the subject of this appeal so they are not very helpful in providing guidance about what the standard should be when evaluating the obviousness of polymorph claims.

In addition, each of the district court decisions that Grünenthal cites is distinguishable. Even though it had a very different factual record, the court in *In re Armodafinil* still assumed that the FDA guidelines provided motivation to do a polymorph screen. 939 F. Supp. 2d 456, 496 (D. Del. 2013). That district court, however, did not rely upon the Byrn protocol nor any other particular protocol to follow for the most readily-available polymorphs, without which the district court held that "trial and error crystallization experimentation is necessary because polymorphs are unpredictable." *Id.* at 497. Similarly in *Merck*, following the traditional prior art method as disclosed in one prior art reference was found not to result in the claimed crystal structure, so it was not obvious to combine with components in other prior art. *Merck & Cie v. Watson Labs, Inc.*, 125 F. Supp. 3d 503, at 512-514 (D. Del. 2015). Finally, *Takeda* is inapplicable at least because the starting material there was an "oil" so it was unknown whether it could even be a

solid. *Takeda Pharmaceutical Co. v. Handa Pharmaceuticals, LLC*, No. C-11-00840 JCS, 2013 WL 9853725, at *74 (N.D. Cal. Oct. 17, 2013). In our case, the '737 patent already disclosed that a solid form of tapentadol "crystallised out." (Appx63; Appx384 at 19:65; Appx9714 at 77:3-6.) And the Byrn reference alone taught how to do the basic polymorph screen, and that was enough to produce Form A tapentadol.

A major distinction from the other district court decisions is the treatment of the Byrn reference. That article disclosed both the motivation to determine whether polymorphs are possible and the routine procedure by which to make that determination. But the district court discounted Byrn anyway—just because it was published before the other district court decisions—even though there was no indication its polymorph screen protocol or test results using that protocol were ever considered by those other district courts. (Appx145.) Grünenthal attempts to support the district court's reliance on cases that did not discuss the Byrn protocol by conflating different portions of the *In re Armodafinil* case. (Resp. Br. at 29-30.) While footnote 43 in that case states references were presented "to provide greater detail as to the state of the art in the early 2000s," Byrn was not one of them. *In re Armodafinil*, 939 F. Supp. 2d at 489 n.43. Byrn was separately cited in footnote 45 for the proposition that the most stable polymorphic form is preferred for drug formulations. *Id*. at 490 n.45. The *Armodafinil* decision did not have the benefit of

the standard prior art protocol, nor the testing using that protocol that resulted in the claimed invention. While Grünenthal argues 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," (Resp. Br. at 34-35), Grünenthal does not identify the "several other pieces of prior art" nor even attempt to describe what they disclosed or what the results of tests using those references revealed.

2. Grünenthal's Own Internal Work Is Irrelevant

Grünenthal spends considerable time emphasizing its own efforts leading to the alleged invention, but that is irrelevant. *See Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("The issue of obviousness is determined entirely with reference to a hypothetical person having ordinary skill in the art. . . . The actual inventor's skill is irrelevant to this inquiry . . . ."); *see also Life Techs., Inc. v. Clontech Lab., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute . . . [T]his inquiry, as a matter of law, is independent of the motivations that led the inventors to the claimed invention."). Accordingly, § 103 requires that the obviousness inquiry must be performed from the perspective of one of ordinary skill in the art, not from the perspective of the inventor. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 420 (2007) ("The question is not whether the

combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art.")

E. The Absence Of Secondary Considerations Supports Obviousness

Plaintiffs argue that they were not required to "rebut Defendants' assertions with objective indicia of nonobviousness" because Defendants did not "establish a prima facie case of obviousness." (Resp. Br. at 53.) With that argument, Grünenthal concedes that so long as Alkem demonstrates prima facie obviousness, Grünenthal has no further evidence to consider. It was Grünenthal's responsibility to offer secondary considerations evidence, if it had any. *See Novo Nordisk A/S v. Caraco Pharm. Labs.*, Ltd., 719 F.3d 1346, 1353 (Fed. Cir. 2013) (ruling it is the patentee's "responsibility to set forth evidence in opposition to a challenger's prima facie case which, if left unrebutted, would be sufficient to establish obviousness.") That is significant because all but one other polymorph case (the district court cases) considered secondary considerations. Here, however, Grünenthal does not have that argument to rely upon.

If Grünenthal had evidence of secondary considerations, it would have provided them, to support the hindsight argument it now makes. After all, the rationale for using secondary considerations is as a "check against hindsight bias." *In re Cyclobenzaprine*, 676 F.3d 1063, 1079 (Fed. Cir. 2012); *see also Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966) (noting objective indicia of

nonobviousness serve to "guard against slipping into use of hindsight."); *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015) ("Objective indicia of nonobviousness can serve as an important check against hindsight bias and 'must always when present be considered.'") (quoting *In re Cyclobenzaprine*, 676 F.3d at 1075-76.) Yet Grünenthal offered no secondary considerations—no commercial success, no unexpected results, and no failure of others that can be linked to this polymorph—that could call the conclusion of obviousness into question or otherwise support Grünenthal's hindsight argument.

III. The Claimed Invention of the '364 Patent Was At Least Obvious To Try

As set forth in Alkem's opening brief, it was at least obvious to try the limited set of crystallization solvents disclosed in the Byrn article as applied to tapentadol hydrochloride, which would result in the claimed Form A. Proving an invention was obvious to try means showing "a design need or market pressure to solve a problem" and "a finite number of identified, predictable solutions" to try. *KSR*, 550 U.S. at 421; (Resp. Br. at 40.). This does not require knowing the results ahead of time, but instead knowing the prior art references and using them for their established intended purpose. Alkem proved both parts of the obvious to try test.

A. The FDA Guidelines Established A Design Need Or Market Pressure To Solve A Problem

Grünenthal does not challenge that there was a design need or market pressure to solve a problem. Indeed, the district court already found that "[a]s early as 1987,

the FDA had issued guidelines indicating that '[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs.'" (Appx139.) The court went on to confirm Grünenthal's admission at trial that "regardless of regulatory guidelines, it was important to know if tapentadol hydrochloride was polymorphic 'not only [for] the regulatory bodies, it was important for any further developments that, to have knowledge of solid form characteristics.'" (Appx140.) Even *In re Armodafinil*, which Grünenthal notes cited the same 1987 FDA guidelines, did not discredit motivation; the opinion "assum[ed] that there would have been a motivation to obtain the most stable form of" the claimed compound." 939 F. Supp. 2d at 497 (internal quotations omitted). The FDA guidance, along with the district court's findings about general industry practice, substantiate the design need and market pressure to identify readily-available polymorphs.

B. The District Court's Findings Below Show that There Were a Finite and Predictable Number of Solutions to Discover Readily-Available Polymorphs

The district court's findings were enough to confirm that there were a finite and predictable number of solutions to discover the readily-available polymorphs for tapentadol, which would have included Form A. The district court, however, never separately addressed the "obvious to try" standard for the polymorph patent. It did determine that "[a] POSA would have understood as of June 2004 how to conduct a polymorph screen and there were publications that provided guidance on

how to do such a screen." (Appx140.) The district court further found that "[i]t is undisputed that the methods for conducting polymorph screening were known in the art." (Appx 145.)

The Byrn article, in turn, identified nine solvents to be used in crystallization experiments specifically to screen for polymorphs. While the result of the screen was not "predictable"—and the district court focused only on that issue—that was not the right legal test. Instead, the test is whether a POSA would expect that the polymorph screen would have worked for its intended purpose, which was to find readily-available polymorphs. *See Pfizer*, 480 F.3d at 1367-68. Here, the district court understood that "[t]he Byrn article states that '[t]he first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question: Are polymorphs possible?'" (Appx141.) And the Byrn article provided the solvents to use in that "first step" screen. *Id*. While not every polymorph is obvious, Form A tapentadol is because there were a limited number of solvents that were being used for their intended purpose to identify readily-available polymorphs.

Because the district court considered predictability to mean the specific properties of the end result (the peaks in an X-ray pattern for Form A), it found the claims nonobvious, but again, that was not the right standard. The district court's determination that "the results of a polymorph screen […] would have been

impossible to predict," is irrelevant to the obvious-to-try analysis. (Appx143-144.) This conclusion ignores *KSR's* "predictability," which is not based on the specific properties of the end result, but rather on the combined prior art references working in the way they were intended to work together. *KSR*, 550 U.S. at 417 (A combination of prior art elements is obvious unless "the improvement is more than the predictable use of prior art elements according to their established functions."); *see also In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (declining to "cabin KSR to the predictable arts" in the face of an unpredictable end result and focusing instead on the "well-known and reliable nature" of the prior art techniques) (internal quotations omitted). To the issue of expected success, Byrn's express goal was to show how to do a polymorph screen and "provide a strategic approach to remove much of [the] uncertainty" "about how to scientifically approach the gathering of information" necessary to comply with the FDA guidelines. (Appx57372-57381 at 57372.)

Though the district court did not separately address obvious to try, nor cite *In re Kubin*, Grünenthal attempts to apply the case at length, but does so incorrectly. That case discussed *O'Farrell* and its "two classes of situations where 'obvious to try' is erroneously equated with obviousness." 561 F.3d 1351, 1359 (citing *In re O'Farrell*, 835 F.2d at 903.) Neither exception to the obvious to try scenario applies here.

1. Polymorph Screens Involved Established Protocols, Not Shots In The Dark

The first class is where one is left in the dark 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." *Id*. Although Grünenthal argues otherwise (Resp. Br. at 42), the district court found that the Byrn article gave more than general guidance and "specifically lists certain solvents to use in the recrystallization experiments." (Appx141.) Byrn identified and narrowed the field to only nine solvents, a finite and discrete number. The district court did hold more generally—without focusing on the Byrn protocol—that polymorph screening "includes 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.) But even as to that general approach, the district never found (and Grünenthal did not argue) that these variables were difficult or outside the realm of a POSA. To the contrary, the district court recognized that solvent crystallization was "one of the first laboratory skills that chemists acquire" and presented "a traditional strategy" to use "a variety of solvents and solvent mixtures." (Appx140-141.) The district court further acknowledged that "[a] POSA would have understood as of June 2004 how to conduct a polymorph screen and there were publications that provided guidance

on how to do such a screen." (Appx140.) That was enough as a matter of law to find the claimed polymorph obvious to try, had the district court addressed it.

2. Polymorph Screens Were Not New By 2004, And Could Be Outsourced

The second *O'Farrell* class where "obvious to try" may not apply is where "what was 'obvious to try' was to 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." 561 F.3d 1351, 1359 (citing *In re O'Farrell*, 835 F.2d at 903.) Polymorph screening was not a new technology or general approach by 2004. To the contrary, the FDA guidance had been published since 1987 (Appx139; Appx57313-57314; Appx 57278), and the Byrn article specifically identified a protocol using nine solvents, to find at least the readily-available polymorphs.

Obtaining the claimed polymorphs would have been at least obvious to try because of the well-established field of polymorphs by 2004 and the limited number of routine solvents for the "traditional" crystallization technique. (Appx59463-59481 at 59466.) "If a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. While not every crystallization in the world would be obvious to try—which is the argument that Grünenthal makes by referring

to theoretically "unlimited" variables—that is not the issue in this case given the particular guidance in the Byrn reference. And the fact that the polymorph screen could simply be outsourced to SSCI in 2004 further confirms that this was not a new field but was already very well established.

Because absolute predictability was not required, the limited number of solvents used for their independent purpose with a screen showed a reasonable expectation of success. *O'Farrell* held that "[o]bviousness does not require absolute predictability of success" and "all that is required is a reasonable expectation of success." 835 F.2d at 903-904. Grünenthal could have tried to show "a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious," but did not attempt to do so. *Id*. at 903.

Grünenthal also relies on *In re Armodafinil*, which concluded that a polymorph was not obvious to try, where the prior art gave general information and no particular guidance. However, as already discussed above, the Byrn article was not used in district court case to identify the routine screening protocol or nine common solvents. The same was true in *Sanofi-Synthelabo v. Apotex, Inc.*, where the accused infringer "did not cite any reference showing or suggesting any reliable method of separation for any analogous compounds." 550 F.3d 1075, 1088 (Fed. Cir. 2008). Similarly, *In re Brimonidine* is inapposite because the prior art taught

that combining the prior art would not work, for various reasons. 643 F.3d 1366, 1376-77 (Fed. Cir. 2011). There is no evidence here that the Byrn protocol would not work in order to obtain the readily-available polymorphs Form A and Form B.

3. Form A Tapentadol Was Inevitable And Obvious To Try

Grünenthal concedes that, at least in some 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." (Resp. Br. at 48.) This is just that case. The Byrn reference gave a confidence that the disclosed protocol and finite number of solvents would reveal the readily-available polymorphs. Form A was nothing more than the result of this obvious work.

Just as in *In re Kubin*, therefore, the asserted polymorph claims are invalid as obvious to try. That case involved an isolated nucleic acid sequence, where one prior art reference identified the general protein of interest and another showed how to identify and recover the gene sequence. 561 F.3d at 1360. Thus, even though the end result may not be completely predictable, combining established technique with a prior art compound supported "a resoundingly 'reasonable expectation of success' in deriving the claimed invention." *Id*. (quotation omitted). The court confirmed that "obvious to try" was not confined to purely "predictable arts," because in any field, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *Id*. at 1360-61 (quoting *KSR*, 550

U.S. at 419.) That is the ultimate proposition in this case: granting Grünenthal with additional patent exclusivity to the tapentadol polymorph, only because it waited to screen the earlier-invented tapentadol compound, represents no real innovation and retards progress.

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitations of Fed. Cir. R. 28.1(b)(1)(A). This brief contains 9,611 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Fed. Cir. R. 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). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in fourteen (14) point Times New Roman font.

Dated: January 31, 2018

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CERTIFICATE OF SERVICE

I, Rose E. Olejniczak, being duly sworn according to law and being over the age of 18, upon my oath deposes and states that:

Counsel Press was retained by SCHIFF HARDIN LLP, Attorneys for Defendant-Appellant Alkem Laboratories Limited, to print this document. I am an employee of Counsel Press.

On January 31, 2018, SCHIFF HARDIN LLP authorized me to electronically file the foregoing Response and Reply Brief of Defendant-Appellant Alkem Laboratories Limited with the Clerk of the Federal Circuit using the CM/ECF System, which will serve e-mail notice of such filing on the following attorneys:

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Upon acceptance by the Court of the e-filed document, I will cause six paper copies of the brief to be filed with the Court, via Federal Express, within the time provided in the Court's rules.

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