No. 24-292

In the Supreme Court of the United States

SALIX PHARMACEUTICALS, LTD., *et al.*,

Petitioners,

v.

NORWICH PHARMACEUTICALS INC.,

Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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BRIEF IN OPPOSITION

Ian Swan
AXINN, VELTROP & HARKRIDER LLP
1901 L Street NW
Washington, DC
20036

Thomas K. Hedemann
Counsel of Record
Matthew J. Becker
Matthew S. Murphy
AXINN, VELTROP & HARKRIDER LLP
90 State House Square
Hartford, CT 06103
(860) 275-8100
thedemann@axinn.com

Counsel for Respondent

CORPORATE DISCLOSURE STATEMENT

Norwich Pharmaceuticals, Inc. is wholly owned by Alvogen Pharma US, Inc. Alvogen Pharma US, Inc. is wholly owned by Alvogen Group, Inc. Alvogen Group, Inc. is wholly owned by Alvogen Holdings (Hungary) LLC. Alvogen Holdings (Hungary) LLC is wholly owned by Alvogen Pharma Ltd. Malta (which is wholly owned by Alvogen Lux Holdings S.à.r.l.).

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INTRODUCTION

The petition provides no basis for this Court's intervention.

First, the petition's fundamental premise – that the majority affirmance is based on an "erroneous approach to appellate review" – is simply incorrect. Pet. 4. Contrary to the petition's assertion, the majority's affirmance was not premised on new fact-finding. Rather, the majority reviewed the district court's findings with respect to the Protocol and Pimentel – the two prior-art references upon which the district court premised its obviousness determination – and concluded that "[t]he district court did not clearly err in finding that a skilled artisan would have looked to both of those references, considered their limits, and had a reasonable expectation of success as to the efficacy of 550 mg TID dosing." Pet. App. 9a. None of the alleged appellate fact-finding forms any part of this analysis and affirmance.

Similarly, the majority did not apply the harmless-error standard the petition contends is improper. That is, the majority did not ask whether it, or a hypothetical fact-finder, would have found a reasonable expectation of success without relying on the Press Release. Pet. 30. Instead, it did exactly as the petition advocates and considered whether the *district court* relied on the Press Release. Pet. App. 13a. Finding that the district court based its holding on the Protocol and Pimentel alone, the majority correctly concluded that it did not need to decide whether or not the Press Release is prior art. Thus,

the panel majority opinion does not exemplify the appellate practices alleged by the petition.

Second, the petition fails to establish that the Federal Circuit regularly engages in the claimed incorrect appellate practices. Two of the three opinions the petition offers as evidence of persistent fact-finding are nearly forty years old, and none of them are convincing examples. Pet. 24-26. Also unpersuasive is the quoted fragment from a speech Judge Lourie gave twenty-four years ago. Pet. 5, 35. By its nature, a speech is at best anecdotal evidence of judicial practice. Here, moreover, the full speech conveys a practice of deference to trial courts' fact-finding.

With respect to the allegedly incorrect standard for harmless error, the petition makes no attempt to establish that this is a recurring issue within the Federal Circuit. Instead, the petition cites one opinion from each of the Ninth, Eighth, and Fourth Circuits as evidence that there is "confusion" about the standard between circuits. Pet. 33-34. These isolated opinions, two of which date from the mid-1990s, do not evidence the application of a different harmless-error standard than the other circuits. Thus, even if the majority opinion had embodied the appellate practices the petition asserts (it does not), the petition fails to establish that those practices are recurrent, important, or representative of a circuit spilt.

Third, although the two reasons referenced above are each independently sufficient to deny the petition, a third reason is that the obviousness determination below is correct. The district court faithfully followed

this Court's framework for analyzing obviousness, determining the scope and content of the prior art, the differences between the prior art and the asserted claims, and the level of ordinary skill in the art. It further considered the alleged secondary considerations of non-obviousness. At the end of that analysis, the district court concluded that the claims are obvious. That conclusion was affirmed by the majority panel, and the Federal Circuit rejected Salix's petition for rehearing and rehearing *en banc*. No further review is warranted.

COUNTERSTATEMENT

1. Salix's patents claim the use of a known drug for a known purpose, i.e., using rifaximin to treat irritable bowel syndrome ("IBS"), including the diarrhea subtype ("IBS-D"). Rifaximin was first discovered in the early 1980s and was used decades before Salix in 2008 filed the application that resulted in the patents at issue. Pet. App. 3a, 76a-77a. In fact, the use of rifaximin to treat IBS was patented by Dr. Mark Pimentel in 1999, almost a decade prior to Salix's application. Pet. App. 76a-77a.

Furthermore, although FDA had not yet formally approved rifaximin for the treatment of IBS, "[t]here is no dispute that skilled artisans knew of the general concept of trying off-label use of rifaximin to treat IBS-D." Pet. App. 12a. Xifaxan 200 mg rifaximin tablets were first approved in the United States in 2004 for the treatment of Traveler's diarrhea. Pet. App. 3a. Soon thereafter, Xifaxan was widely prescribed for off-label treatment of IBS, including IBS-D. Pet. App. 76a. In 2005, for example, Dr. Pimentel disclosed at a conference that his

practice group had used rifaximin to treat about 900 patients for IBS. Pet. App. 77a, CAFedAppx7344-7345. That off-label practice only continued to grow. "Prescription data showed that 27.7% of Xifaxan 200 mg tablet uses in November 2007 had been for IBS." Pet. App. 76a. And "[a]s of January 2008, 74% of gastroenterologists polled by Salix had prescribed Xifaxan for IBS." *Id.*

In view of this widespread off-label use of rifaximin to treat IBS, it is unsurprising that the prior art discloses clinically effective off-label uses of rifaximin to treat IBS, including IBS-D. The district court found that, "[i]n 2006, Dr. Pimentel published a book titled *A New IBS Solution, Bacteria – the Missing Link in Treating Irritable Bowel Syndrome*, which recommended the use of rifaximin as a safe and effective way to treat IBS-D." Pet. App. 77a. Others had published retrospective studies concerning the use of rifaximin to treat IBS and symptoms thereof. Pet. App. 77a-78a. For example, Cuoco published "[a] retrospective chart review of IBS patients who had tested positive for small intestine bacterial overgrowth ('SIBO') reported a significant reduction in the number of patients having IBS symptoms 4-5 months after treatment, and that 12 of 23 patients had 'complete resolution of IBS symptoms.'" Pet. App. 77a.

The only allegedly novel aspect of Salix's patents is the claimed dosage amount of 550 mg, three times per day ("TID"), for a total of 1,650 mg/day. Pet. App. 6a. However, and as the district court found, this too was known: "Pimentel 2006 reported sustained improvement in IBS symptoms for patients aged 18-

65 for at least 10 weeks on a 400 mg TID, 10-day regimen." Pet. App. 79a. And the Protocol disclosed "a 14-day dosing regimen of 550 to 2200 mg per day, and the treatment of patients with IBS-D in particular." *Id.*

2. Following a four-day bench trial, the district court found that "[t]he RFIB 2001 Protocol and Pimentel 2006 disclose all limitations of the asserted IBS-D claims." Pet. App. 8a, 78a. The district court further found that "[a] POSA would have been motivated to combine the RFIB 2001 Protocol and Pimentel 2006 with a reasonable expectation of success." Pet. App. 73a, 79a. Based on these findings, and after considering the alleged secondary considerations of non-obviousness, the district court concluded that the asserted claims are invalid as obvious over the combination of the Protocol and Pimentel. Pet. App. 78a, 87a.

3. The only aspect of the district court findings that Salix appealed was that a POSA would have had a reasonable expectation of success in combining the Protocol and Pimentel. Pet. App. 8a. The panel majority found no clear error in the district court's finding of a reasonable expectation of success and consequently affirmed. Pet. App. 8a-10a. As the majority explained, "[t]he Protocol provides an outline of a planned Phase II clinical trial in which 'three different doses (275, 550 and 1100 mg) of rifaximin' were to be 'administered BID [i.e., twice-daily] for either two or four weeks in the treatment of patients with diarrhea-associated irritable bowel syndrome.'" Pet. App. 8a. It thus disclosed a range of 550 mg to 2,200 mg rifaximin per day to treat IBS-D. The

majority further noted that "Pimentel teaches that administration of 400 mg rifaximin, TID (1,200 mg/day), 'resulted in greater improvement in IBS symptoms' and 'lower bloating score[s] after treatment.'" Pet. App. 9a. "Pimentel further teaches that '[r]ecent data suggest that the optimal dosage of rifaximin may, in fact, be higher than that used in our study.'" Pet. App. 9a. As the petition does not dispute, all the disclosures and teachings from the Protocol and Pimentel referenced by the panel majority are findings by the district court. *Compare* Pet. App. 7a-10a *with* Pet. App. 76a-79a.

4. On June 13, 2024, the Federal Circuit denied Salix's petition for rehearing or rehearing *en banc*.

REASONS FOR DENYING THE PETITION

I. THE PANEL MAJORITY OPINION DOES NOT EMBODY THE ALLEGED INCORRECT APPELLATE PRACTICES

A. The Panel Majority Did Not Base Its Affirmance on the Asserted Fact-Finding.

The premise for the petition's first question is the proposition that the panel majority "affirmed a judgment based on evidence never credited by the district court." Petition at i. Specifically, the petition contends that the affirmance relies on (1) a finding by the majority that SIBO is a cause of IBS-D, and (2) the prior art references Lauritano, Scarpellini, and Lin. Pet. 19-20. This contention is wrong and based on a misreading of the panel opinion.

The majority opinion begins by setting out the standard of review, which is *de novo* for the ultimate legal question of obviousness and clear error for the underlying factual determinations. Pet. App. 5a-6a. After reviewing the asserted patent claims, the opinion provides an overview of the Protocol and Pimentel – the two key prior art references – before recounting that "[t]he district court found that those two reference disclose each and every limitation of the challenged IBS-D claims, and further found that a skilled artisan would have been motivated to combine those two references to arrive at what is claimed with a reasonable expectation of success." Pet. App. 7a (citing trial opinion). It further observes that there is no dispute that the two references disclose every limitation, and that Salix's appeal was based only on an argument that there was insufficient evidence to support a finding of reasonable expectation of success. *Id*.

Having established the framework for the appeal, the panel majority then considers Salix's argument by reviewing the district court's findings pertaining to the Protocol and Pimentel. Pet. App. 8a-9a. Finding no issues with those findings, it concludes that "[w]e see no clear error in the conclusion that there would have been a reasonable expectation of success in administering the claimed 1,650 mg/day to IBS-D patients." Pet. App. 9a-10a.

Plainly, the majority's discussion does not touch on SIBO or any of the Lauritano, Scarpellini, and Lin references, but is focused solely on the district court's findings with respect to the Protocol and Pimentel. And it is based upon those findings that the majority

concludes that the district court did not clearly err in finding a reasonable expectation of success.[1] There is consequently no basis for the petition's contention that the affirmance was based on the new fact-finding.

The majority's discussion of SIBO and additional prior art only occurs *after* the affirmance. Pet. App. 10a-12a. Indeed, it is evident that this discussion is intended to show that the conclusion already reached is further supported by additional record-evidence. *See* Pet. App. 10a (stating that references establishing the background knowledge of the skilled person "*are consistent with* the reasonable expectation of success provided by the combination of the Protocol with Pimentel.") (emphasis added); Pet. App. 11a (stating that "[t]he record *further supports* the finding that there would have been a reasonable expectation of success. . . .") (emphasis added). Again, the claim that the discussion of SIBO and related prior art formed the basis for the affirmance is factually incorrect.

Additionally, it is not true that the majority made some new finding about the relationship between SIBO and IBS-D. Pet. 16. On the contrary, the majority states that it "agree[s] with the district court that references describing the treatment of SIBO would have been pertinent to [a reasonable expectation of success]." Pet. App. 10a-11a. And

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[1] The petition references the dissent's argument that the district court relied on Pimentel's teaching concerning the optimal dosage of rifaximin in the motivation-to-combine analysis rather than in the reasonable-expectation-of-success analysis. Pet. 15. As the majority undoubtedly saw, however, the district court did not so neatly divide the analyses and the Pimentel statement served both. *See* Pet. App. 79a-81a.

there can be no dispute that the district court found the such reference would have been "pertinent." For example, the district court stated that it was "unpersuaded" by Salix's argument that a person of skill would discount SIBO-related references because it was unproven that SIBO contributed to IBS-D. Pet. App. 82a. Indeed, the district court could not have been more clear: "I do not think a POSA would have discounted prior art sources that were based upon the theory that SIBO contributed to IBS because studies such as the RFIB 2001 Protocol were testing that hypothesis at the time." Pet. App. 84a-85a. In this context, finding that a POSA would not "discount" the SIBO references is no different than finding that the references would have been "pertinent." Thus, contrary to the petition's assertion, the panel majority did not "[take] it upon itself to make a finding about the relationship of SIBO and IBS-D. . . ." Pet. 16.[2]

B. The Panel Majority Did Not Apply the Alleged Incorrect Standard for Harmless Error.

The premise for the petition's second question is the proposition that the panel majority applied a harmless-error standard that asked "whether the majority would (or a hypothetical factfinder could) have reached the same result without relying on the press release." Pet. 30. Specifically, the petition asserts that "[t]he panel majority held that the

[2] It is unclear how Salix can challenge that POSAs had reason to believe that there is a connection between SIBO and IBS given that Salix itself licensed and listed the Pimentel patents (now prior art) that explicitly describe this connection on the label of its Xifaxan 550 mg product for the treating of IBS-D. Pet. App. 76a-77a, CAFedApxx3070-3071, CAFedAppx3138-3139.

district court's reliance on the press release was harmless because, *based on the panel's findings*, other evidence 'established the obviousness of the claims.'" Pet. 29 (emphasis added). That assertion, however, bears little resemblance to the majority's actual holding:

> Although the district court cited the Press Release in its discussion of the skilled artisan's expectations, it ultimately held that the "Protocol and Pimentel [ ] disclose all limitations of the IBS-D claims" and that a skilled artisan "would have been motivated to combine the . . . Protocol and Pimentel [ ] with a reasonable expectation of success." Decision at *17. We therefore need not decide whether or not the Press Release was prior art because, even assuming that it was not, the Protocol and Pimentel alone established the obviousness of the claims.

Pet. App. 13a. Far from inserting its own findings into the harmless-error analysis, the majority explained that the *district court* reached its obviousness conclusion on the basis of the Protocol and Pimentel alone and that *therefore* it was unnecessary to the review whether the Press Release is prior art.

In sum, the majority applied the standard the petition advocates as appropriate, i.e., to ask whether the Press Release affected the district court's analysis. Pet. 30. And in posing that question, the panel majority correctly concluded that the absence of

the Press Release would not affect the district court's conclusion. The majority thus determined that it did not need to resolve the prior-art status of the Press Release.

II. THE PETITION FAILS TO SHOW THAT THE FEDERAL CIRCUIT "OVERSTEPS" THE LIMITS OF APPELLATE REVIEW

As already discussed, the petition's contention that the panel majority "overstepped" the limits of appellate review is based on a misreading of the majority opinion. This alone warrants denial of the petition. But even if the majority opinion could somehow be read as embodying the sins that the petition alleges, the petition fails to demonstrate they are recurrent, important, or represent a circuit split such that intervention from this Court could be warranted.

A. The Petition Does Not Demonstrate That the Federal Circuit Persistently Engages in Inappropriate Fact-Finding.

The petition cites a total of three opinions – two of which are nearly four decades old – to support its contention that the Federal Circuit practices an "erroneous approach to appellate review. . . ." Pet. 24. They do not.

In *Medtronic, Inc. v. Daig Corporation*, 789 F.2d 903 (Fed. Cir. 1986), the appellant argued that the trial court analyzed the prior art references individually and "failed to consider the references as a whole." *Id.* at 906. In rejecting that argument, the Federal Circuit observed that the trial court had

"conducted a thorough analysis of the prior art" and explicitly found that none of them "*either alone or in combination,* would have taught, disclosed, or suggested [the claimed invention]." *Id.* n.7 (emphasis in original). Thus, the *Medtronic* panel neither engaged in fact-finding nor resolved any unresolved factual disputes, the "oversteps" the petition asserts are common. Indeed, this Court may have recognized as much when it denied the subsequent petition for certiorari. *Daig Corp. v. Medtronic, Inc.*, 479 U.S. 931 (1986).

In the second cited opinion, *FMC Corporation v. Hennessy Industries, Inc.*, the panel rejected an argument that the district court had erroneously applied an "on hand" test for determining the "on sale" question because it had failed to consider a distribution agreement and certain other record evidence. 836 F.2d 521, 524 (Fed. Cir. 1987). In rejecting this argument, the panel stated that "failure to mention does not mean failure to consider when the evidence supplies support for the district court's determination." *Id.* Petitioner offers this as evidence of fact-finding but overlooks the panel's full discussion:

> FMC has not shown the presence of clear error in the district court's findings that: (a) Tabordon did not recognize the relevance of the semi-power machine; and (b) that Tabordon and attorney Wood believed March 14, 1961 to be the earliest conceivable sale of the full-power machine. FMC says clear error occurred when the district court did not draw the

> inferences FMC would have us draw from [the distribution agreement and other evidence]. We find, however, nothing in the record that would preclude the district court from drawing such inferences as may be encompassed in the findings it made. Thus, FMC has not shown any district court finding to have been clearly erroneous.

Id. at 524-25 (citation omitted). Thus, far from crediting evidence that had not been credited below, the panel considered the appellant's arguments and found that they failed to demonstrate any clear error with the *district court's* findings. Indeed, in doing so, the panel cited *Anderson v. City of Bessemer City, N.C.*, where this Court explained that "[w]here there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous." 470 U.S. 564, 574 (1985).

The petition finally cites *IQASR LLC v. Wendt Corporation*, 825 F. App'x 900 (Fed. Cir. 2020). While it is unclear why the panel in this nonprecedential opinion chose to discuss the testimony of Wendt's expert, it *is* clear that the panel did not rely on that testimony for its affirmance of the trial court's conclusion that the term "magnetic fuzz" was indefinite. *See id.* at 903-08 (reviewing the district court's findings, the intrinsic evidence, and appellant's arguments, and finding no clear error).

The petition also cites a fragment of a speech given by Judge Lourie some twenty-four years ago. Pet. 5, 35. It omits the context for the fragment, however, as well as other relevant portions of the

speech. In the part of the speech from which petitioner cites, Judge Lourie addresses criticisms of the Federal Circuit's reversal rate and states that an implication of the criticism is that "we engage in improper appellate fact-finding." Judge Alan D. Lourie's Speech to the PTC Section of the D.C. Bar (June 12, 2000), *in* 60 Pat. Trademark & Copyright J. 147 (June 16, 2000), at 148. But far from endorsing such appellate fact-finding as standard Federal Circuit practice, Judge Lourie states that he does not believe the allegation is "well-founded in general" and that the "data bear me out." *Id.* He goes on to praise the work of trial courts and to explain that his "approach is to defer . . . unless I have a firm conviction that an error has been made. . . ." *Id.*

Furthermore, the fragment cited by the petition occurs in the context of a discussion of *intrinsic* patent evidence:

> A critical fact in patent appeals i[s] that much of the result of a patent case hinges on what the patent states, and we have the patent before us just as the district court judge has. Although what a patent states is of course a fact question, overcoming deference more readily occurs when we can read and understand the patent and conclude that the fact finder clearly erred or had no reasonable basis for its conclusion. *And while in a particular case, one might consider that a remand rather than a reversal is in order, we hesitate to send a*

> *case back to the district court when it is plain to us what the result would be.*

Id. (sentence quoted by petition emphasized). At most, this discussion merely embodies the exception to remand when "the record permits only one resolution of the factual issue." *Pullman-Standard v. Swint*, 456 U.S. 273, 292 (1982). Thus, rather than support the petition's assertion of a practice of appellate overreach, Judge Lourie's speech demonstrates his conviction that the Federal Circuit should employ (and was employing at the time) the very principles of appellate practice that the petition advocates.

B. The Petition Does Not Demonstrate That the Federal Circuit Applies an Incorrect Harmless-Error Standard or That There Is "Confusion" About the Standard In Other Circuits.

As discussed above, the panel majority did not apply the harmless-error standard the petition asserts is improper. Furthermore, even if the panel majority *had* done so in this instance, the petition fails to cite even a *single* other opinion in which the Federal Circuit has applied that standard. Plainly, therefore, the petition falls far short of demonstrating that this is the type of recurring issue in the Federal Circuit that could warrant review by this Court.

The petition's attempt to establish that there is "confusion" about the standard in other circuits is equally unconvincing. Pet. 33-34. The petition first cites opinions from the majority of the circuits that, according to the petition, apply the standard the

petition advocates. Pet. 30-31 (citing opinions from the First, Fourth, Fifth, Sixth, Eighth, Tenth, and Eleventh Circuits). The petition's assertion of confusion is based on solitary opinions from each of the Ninth, Eighth, and Fourth Circuits. Pet. 33-34. The first is *Crawford v. Hawaii*, 87 F.3d 1318, (9th Cir. 1996), a nearly 30-year old unpublished opinion. Although the early part of the opinion contains the language the petition emphasizes, it later reviews a similar evidentiary issue and finds it to be harmless error "[b]ecause the trial court more probably than not would have reached the same conclusions if the original notes had been admitted instead of the photocopies." *Id*. at *2. It is thus far from clear whether or not the Ninth Circuit applied the allegedly incorrect standard in this solitary opinion.

The next is *Delph v. Dr. Pepper Bottling Company of Paragould, Inc.*, 130 F.3d 349 (8th Cir. 1997), another decades-old opinion. In that case, the issue concerned an "objective inquiry—whether a reasonable person would find the Dr. Pepper workplace hostile. . . ." *Id.* at 355. As the petition admits, the Eighth Circuit did not fully articulate its reasoning in finding that the evidence were sufficient to meet this objective test. Pet. 33. Given the nature of the evidence recited in the opinion, however, the panel may have considered it sufficient to satisfy the objective test as a matter of law. Thus, based on this lone opinion it cannot be concluded that the Eight Circuit is "confused" as to the standard for harmless error. This is all the more true given that the petition itself cites two Eight Circuit opinions as examples where the purportedly correct standard for harmless error was applied. Pet. 30-31.

Lastly, the petition contends that it "appears" that the Fourth Circuit failed to apply the standard advocated by the petition in *Israelitt v. Enterprise Services LLC*, 78 F.4th 647 (4th Cir. 2023). But it equally "appears" that the Fourth Circuit *did* apply that standard. After reciting a number of factual findings made by the district court and stating that those findings "receive clear-error review," the court concluded: "Even if the performance review was inadmissible evidence the court should not have considered, we cannot say that the district court clearly erred in holding that Israelitt could not establish causation." *Id.* at 661-62. Based on this language, the Fourth Circuit may well have done as the petition advocates and considered whether the district court's conclusion would have remained the same absent the evidence. Indeed, the petition contends that the Fourth Circuit did apply that standard in an earlier opinion. Pet. 30.

In sum, the three solitary opinions cited by the petition fail to demonstrate any systematic "confusion" in the circuits as to the standard for harmless error.

III. THE OBVIOUSNESS DETERMINATION IS CORRECT

For the reasons already given, the petition provides no basis for this Court's review. A still further reason why certiorari should not be granted is that the obviousness determination below is correct.

"Section 103(a) forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (quoting 35 U.S.C. § 103). "[A]s progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts." *Id.* at 427. This Court has provided the following framework for analyzing obviousness:

> Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the art resolved. Against this background, the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Id. (quoting *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)).

Here, the asserted patents claim merely an obvious variant of a method long-known to skilled artisans. Prior to 2008, Dr. Pimentel had patented the use of rifaximin to treat IBS, physicians had prescribed rifaximin to treat thousands of IBS-D

patients, and the prior art disclosed the successful use of rifaximin to treat IBS, including IBS-D, as well as dosages encompassing those claimed. *Supra*, at 3-4. The prior art thus taught the use of rifaximin to treat IBS-D. Pet. App. 76a-77a.

With respect to the claimed dosing amounts – the only conceivably novel aspect of the claims – the district court found that "Pimentel 2006 reported sustained improvement in IBS symptoms for patients aged 18-65 for at least 10 weeks on a 400 mg TID, 10-day regimen." Pet. App. 79a. It also found that "[t]he RFIB 2001 Protocol included no upper age limit, a 14-day dosing regimen of 550 to 2200 mg per day, and the treatment of patients with IBS-D in particular." *Id*. The district court thus determined that "[t]he RFIB 2001 Protocol and Pimentel 2006 disclose all limitations of the asserted IBS-D claims." Pet. App. 8a, 78a. Salix did not appeal this finding.

The district court further found that "a POSA would have been motivated to combine Pimentel 2006 with the RFIB 2001 Protocol and would have had a reasonable expectation of success." Pet. App. 79a. The panel majority agreed, concluding that "[t]he district court did not clearly err in finding that a skilled artisan would have looked to both of those references, considered their limits, and had a reasonable expectation of success as to the efficacy of 550 mg TID dosing." Pet. App. 9a. That is because "[t]he combined message that the skilled artisan would have discerned from the Protocol and Pimentel is that the optimal dosage for treating patients suffering from IBS disorders may be higher than

400 mg TID, and the next higher dosage unit from the Protocol was 550 mg." *Id.*

Turning to secondary considerations, the district court found that "[t]he prior art did not teach away from using rifaximin to treat IBS-D according to the claimed methods." Pet. App. 73a; *see also* Pet. App. 84a ("Quigley, Vanner, and Drossman do not teach away from using rifaximin to treat IBS, and Salix does not argue that they do."). And Salix offered no evidence or argument that the claimed dosing regimen achieved any unexpected or surprising result. Finally, the district court weighed Salix's alleged evidence of skepticism and determined that "Salix has shown a small amount of skepticism but not enough to change the outcome of the obviousness analysis." Pet. App. 87a. Salix did not appeal any issue concerning secondary considerations.

In sum, the district court correctly applied the framework set forth in *Graham* and *KSR* and concluded that the asserted patents are invalid for obviousness. Finding no clear error in the district court's underlying factual findings, the panel majority correctly upheld the invalidity determination.

CONCLUSION

For the foregoing reasons, this Court should deny the petition for writ of certiorari.

Respectfully submitted,

Ian Swan
AXINN, VELTROP & HARKRIDER LLP
1901 L Street NW
Washington, DC 20036

Thomas K. Hedemann
Counsel of Record
Matthew J. Becker
Matthew S. Murphy
AXINN, VELTROP & HARKRIDER LLP
90 State House Square
Hartford, CT 06103
(860) 275-8100
thedemann@axinn.com

Counsel for Respondent

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