No.

In the Supreme Court of the United States

VANDA PHARMACEUTICALS INC.,

Petitioner,

v.

TEVA PHARMACEUTICALS USA, INC.;
APOTEX INC.; APOTEX CORP.,

Respondents.

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

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Section 103 of title 35 of the U.S. Code provides that an invention is not patentable if it "would have been obvious" to a person of ordinary skill in the relevant art. In *KSR International Co.* v. *Teleflex, Inc.*, this Court explained that a "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 550 U.S. 398, 416 (2007).

The Federal Circuit, based on its own longstanding rule, holds that a combination of known elements is obvious where an ordinarily skilled artisan would have a "reasonable expectation of success" in reaching the resulting invention. Applying that rule here, the Federal Circuit concluded that the mere existence of a clinical trial and long-existing general FDA guidance would contribute to a skilled artisan's reasonable expectation of success, rendering the results of the ensuing experimentation unpatentable, no matter how innovative or unpredictable the results.

The question presented is:

Whether obviousness requires a showing of "predictable" results, as this Court held in *KSR*, or a mere "reasonable expectation of success," as the Federal Circuit has held both before and after *KSR*?

CORPORATE DISCLOSURE

Petitioner Vanda Pharmaceuticals Inc. discloses that it has no parent corporation and that BlackRock Fund Advisors owns more than 10% of its stock.

RELATED PROCEEDINGS

Vanda Pharms. Inc. v. *Teva Pharms. USA, Inc.*, No. 23-1247 (Fed. Cir. May 10, 2023)

Vanda Pharms. Inc. v. *Teva Pharms. USA, Inc.*, Nos. 18-cv-651, 18-cv-689, 19-cv-560, 19-cv-685, 1:19-cv-2202, 19-cv-2375, 20-cv-83, 20-cv-93, 20-cv-1104, 20-cv-1333, 21-cv-121, 21-cv-282 (D. Del. Dec. 13, 2022)

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PETITION FOR A WRIT OF CERTIORARI

Petitioner Vanda Pharmaceuticals Inc. respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit in this case.

OPINIONS BELOW

The court of appeals' opinion (App., *infra*, 1a-16a) is unreported but available at 2023 WL 3335538. The district court's decision (App., *infra*, 17a-75a) is unreported but available at 2022 WL 17593282.

JURISDICTION

The court of appeals entered judgment on May 10, 2023, and denied a timely filed petition for rehearing on August 16, 2023. On October 18, 2023, the Chief Justice extended the time to file a petition for certiorari to January 12, 2024. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISION INVOLVED

35 U.S.C. § 103 states in relevant part:

> A patent for a claimed invention may not be obtained * * * if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

STATEMENT

Patents are essential property rights—provided for in the Constitution and secured by the Patent Act. *Consolidated Fruit-Jar Co.* v. *Wright*, 94 U.S. 92, 96

(1876) ("A patent for an invention is as much property as a patent for land."). By securing innovators' returns on their investments in research and development, patents are essential to "exploit the full potential of our inventive resources." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989).

To be patentable, an invention cannot have been "obvious" to a person of ordinary skill in the art at the time it was made. 35 U.S.C. § 103. In *KSR International Co.* v. *Teleflex, Inc.*, the Court held that a "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 550 U.S. 398, 416 (2007). This standard was long adopted in the regional circuits prior to the creation of the Federal Circuit, and it accords with the Court's longstanding pronouncements about the contours of obviousness—that claims are invalid as obvious only where the result would have been "perfectly plain" (*Dow Chem. Co.* v. *Halliburton Oil Well Cementing Co.*, 324 U.S. 320, 327 (1945)) or "immediately recogniz[able]" to one skilled in the art (*De Forest Radio Co.* v. *General Elec. Co.*, 283 U.S. 664, 682 (1931)).

The Federal Circuit, however, has charted its own course. Rather than pegging obviousness to "predictable results," that court instead holds that a combination of known elements is obvious when an ordinarily skilled artisan would have a "reasonable expectation of success" in the results reached. As this case illustrates, a "reasonable expectation of success" is a far lower standard than that adopted by this Court. In the case of pharmaceutical innovation (like other chemical arts and scientific pursuits), innovation often relies on incremental experimentation to achieve

breakthroughs. While many experiments fail, the prior art often contains some references that could lead a skilled artisan to "reasonably expect" the outcome of the next experiment that happens to be successful—indeed, that is why innovators invest millions of dollars into conducting the experiment. A skilled artisan will often have a "reasonable expectation of success" long before one could ever conclude that a result is "predictable."

The Federal Circuit's incorrect test for obviousness has a significant effect on patent law throughout the country. Most relevant here, it threatens to render many advancements in drug development unpatentable. That is an especially pernicious result for rare diseases, where patent-based incentives are crucial for innovators to invest the billions required to develop new, successful treatments.

The Federal Circuit's improper standard led to the wrong result here. For example, the Federal Circuit invalidated Vanda's patent disclosing a method of using the drug tasimelteon to treat Non-24-Hour Sleep-Wake Disorder (Non-24), based in substantial part on Vanda's disclosure of clinical trials it was undertaking, and which ultimately supplied the results necessary to secure the patent. Although clinical trials often fail, the court of appeals used this as evidence that a person of ordinary skill in the art would have a "reasonable expectation of success." If, however, the court had applied the correct "predictable results" standard, it could not have concluded that this evidence supports a finding of obviousness.

In all, the Federal Circuit employs an obviousness standard that materially departs from this Court's longstanding holdings. That different standard mat-

ters immensely—and it was dispositive here. Further review is warranted.

A. Legal background

1. The patent laws "'promote the Progress of * * * useful Arts, by securing for limited Times to * * * Inventors the exclusive Right to their * * * Discoveries.'" *Graham* v. *John Deere Co. of Kansas City*, 383 U.S. 1, 5 (1966) (quoting U.S. Const. art. I, § 8, cl. 8). A patent operates as "a reward, an inducement, to bring forth new knowledge" by granting the right to exclude others for its term. *Id.* at 9. It incents "[i]nnovation, advancement, and things which add to the sum of useful knowledge." *Id*. at 6. But limitations are necessary to "weed[] out those inventions" that are not "new and useful innovations." *Id.* at 9, 11.

One limitation is nonobviousness, which has been reflected in the Court's precedent for more than 170 years. See *Graham*, 383 U.S. at 11. The nonobviousness criterion reflects the principle that "the difference between the new thing and what was known before [must be] considered sufficiently great to warrant a patent." *Id.* at 14 (quoting S. Rep. No. 82-1979 (1952); H.R. Rep. No. 82-1923 (1952)).

Over the ensuing decades, the Court described a claimed invention as obvious when it would have been "perfectly plain to an expert" (*Dow Chem.*, 324 U.S. at 327), or "immediately recognized" and "found ready at hand" by one skilled in the art (*De Forest Radio*, 283 U.S. at 682, 685), or "plainly indicated," or "plainly foreshadowed" (*Textile Mach. Works* v. *Louis Hirsch Textile Machs.*, 302 U.S. 490, 497-498 (1938)).

The Court has been careful to distinguish obvious inventions from those inventions where elements

were present in the prior art, but the combination of them produced a "new and beneficial result." *Webster Loom Co.* v. *Higgins*, 105 U.S. 580, 591 (1881). This is essential to prevent hindsight bias: It "is often the case with inventions of the greatest merit" that, after "it has succeeded, it may seem very plain to any one that he could have done it as well." *Ibid*. To guard against improperly denying patent protection, the Court has long explained that, "if a new combination and arrangement of known elements produce a new and beneficial result, never attained before, it is evidence of invention." *Ibid*.

In 1952, Congress codified the Court's nonobviousness doctrine via Section 103 of the Patent Act. It provides that an invention is not patentable if that invention would have been "obvious" at the time it was made to a person having ordinary skill in the art. 35 U.S.C. § 103. See also *Graham*, 383 U.S. at 14-17.[1]

This Court construed the newly codified standard in *Graham*, prescribing three basic factual inquiries:

> [T]he 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 pertinent art resolved.

383 U.S. at 17. "Against this background," *Graham* held, "the obviousness or nonobviousness of the subject matter is determined," a determination that may be informed by "secondary considerations [such as]

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[1] Amendments to Section 103 in the Leahy–Smith America Invents Act (AIA) (Pub. L. No. 112-29 § 3(c), 125 Stat. 284, 287 (2011)) have not altered the Federal Circuit's approach to the governing obviousness standard. See, *e.g.*, *Yita LLC* v. *MacNeil IP LLC*, 69 F.4th 1356, 1363 n.3 (Fed. Cir. 2023).

commercial success, long felt but unsolved needs, failure of others, etc." *Ibid.*

In *KSR*, the Court reaffirmed that "the[se] factors define the controlling inquiry." 550 U.S. at 399. It observed, in line with longstanding precedent, that a "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. Accord *Dow Chem.*, 324 U.S. at 327 ("perfectly plain to an expert"); *Textile Mach.*, 302 U.S. at 498 ("plainly foreshadowed"); *De Forest Radio*, 283 U.S. at 682 ("immediately recognized"). Stated another way, *KSR* instructed that a "court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." 550 U.S. at 417.

2. Meanwhile, the U.S. Court of Customs and Patent Appeals (CCPA) fashioned its own obviousness formulation. The CCPA concluded that an invention is obvious where a skilled artisan would understand that "there is at least a reasonable expectation of success." *Application of Mehta*, 347 F.2d 859, 865 (C.C.P.A. 1965). See also *Application of Clinton*, 527 F.2d 1226, 1228 (C.C.P.A. 1976) (holding that, for obviousness, "a reasonable expectation of success is necessary").[2]

Following its formation, the Federal Circuit incorporated the CCPA's standard into its own case law,

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[2] Similarly, the Board of Examiners determined that "merely appl[ying] an old process to another analogous material with at least reasonable expectation of success" "does not constitute invention." *Commonwealth Eng'g Co. of Ohio* v. *Watson*, 188 F. Supp. 544, 545 (D.D.C. 1960).

observing that "[o]nly a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness." *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985).

Before this Court's decision in *KSR*, the Federal Circuit employed the reasonable-expectation-of-success formulation as part of a two-step inquiry. According to that court, "[s]ubsumed within the *Graham* factors is a subsidiary requirement articulated by this court that where * * * all claim limitations are found in a number of prior art references," a patent challenger needs to show "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

In *KSR*, this Court rejected the Federal Circuit's "rigid" application of the teaching-suggestion-motivation (or TSM) test and reaffirmed the "functional approach" of *Graham*. 550 U.S. at 415, 419. It criticized the Federal Circuit's "transform[ation]" of a "general principle into a rigid rule that limits the obviousness inquiry." *Id.* at 419.

Following *KSR*, the Federal Circuit has continued to adhere to its "subsidiary requirement" "subsumed within the *Graham* factors" (*Pfizer*, 480 F.3d at 1361)—that obviousness turns on whether a skilled artisan would have "been motivated to combine the teachings of the prior art references" and would have had a "reasonable expectation of success" in achieving the patented result. See, *e.g.*, App., *infra*, 15a; *Elekta Ltd.* v. *ZAP Surgical Sys., Inc.*, 81 F.4th 1368, 1377 (Fed. Cir. 2023).

B. Factual background

This case concerns tasimelteon—the first drug that FDA approved to treat two different rare conditions: Non-24-Hour Sleep-Wake Disorder (Non-24), a debilitating circadian-rhythm disorder that disproportionately afflicts individuals who are totally blind (App., *infra*, 2a-3a), and nighttime sleep disturbances in individuals with Smith-Magenis Syndrome, a rare genetic neurodevelopment disorder (C.A. App. 19173).

Vanda is a pharmaceutical company focused on the development and commercialization of innovative therapies to address high-priority unmet medical needs and improve the lives of patients. As one way of carrying out its mission, Vanda acquires molecules that other companies have abandoned and, through ingenuity and great expense, investigates new uses for them. See, *e.g.*, C.A. App. 19027-19028.

That is the story of tasimelteon. Bristol-Myers Squibb (BMS) tried but failed to develop tasimelteon into an approvable treatment for insomnia in elderly patients. C.A. App. 19027. After a lack of success, BMS abandoned development of tasimelteon, and Vanda licensed the molecule in 2004 for a small token payment and the promise of future milestone payments. *Id.* at 19027-19028.

Through painstaking, significant, and costly clinical testing, Vanda developed the drug into a useful therapeutic. Vanda studied tasimelteon in the treatment of jet-lag-type sleep disorder and shift-work sleep disorder. C.A. App. 19027-19028. Vanda also studied tasimelteon for treatment of Non-24, designing the largest-ever study of treatment of Non-24 in blind people. *Id.* at 19038-19039. Vanda's studies showed that tasimelteon could entrain (meaning

synchronize with the 24-hour day) the circadian rhythms of blind people with Non-24, where no FDA approved product had worked before. *Id.* at 19030-19031, 19300-19301. Vanda also conducted extensive research to determine the appropriate dosage and the appropriate timing of administration needed to entrain a Non-24 sufferer's circadian rhythm to the 24-hour day. *Id.* at 19031-19033. And Vanda studied the metabolization of tasimelteon and determined that tasimelteon interacts poorly with certain other drugs that inhibit or induce certain key liver enzymes (called CYP1A2 and CYP3A4). *Id.* at 19034, 23040. Finally, Vanda determined through clinical experimentation that food significantly decreases the amount of tasimelteon available in the short, sharp pulse needed to entrain a person's circadian rhythm, and therefore tasimelteon should be administered without food. *Id.* at 19034, 23168.

Vanda's clinical studies—performed at considerable expense and over many years—enabled Vanda to secure FDA approval in 2014 for Hetlioz® as the first-ever therapy to treat Non-24. C.A. App. 19293; App., *infra*, 18a.

The patents at issue in this case reflect Vanda's clinical work developing tasimelteon; they cover:

- tasimelteon's unexpected efficacy in entraining a Non-24 patient's circadian rhythm when administering a 20mg dose an hour before bedtime (U.S. Patent No. RE46,604 (the RE604 patent) (C.A. App. 77-118)),
- tasimelteon's previously unknown interaction with certain classes of drugs and method of discontinuing treatment with those drugs before administering tasimelteon (U.S. Patent

Nos. 9,730,910 and 10,149,829 (the '910 and '829 patents) (*id.* at 119-159, 160-194)), and

- tasimelteon's unpredicted need to be administered without food (U.S. Patent No. 10,376,487 (the '487 patent) (*id.* at 195-198)).

C. Proceedings below

Respondents Teva and Apotex are generic drug manufacturers. Each filed an abbreviated new drug application (or ANDA) with the FDA seeking approval to market generic tasimelteon to treat Non-24 and, pursuant to the Hatch-Waxman Act, notified the FDA and Vanda that they intended to challenge the patents' validity. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV), (j)(2)(B). Vanda accordingly sued for patent infringement. App., *infra*, 3a. See also 21 U.S.C. §355(j)(5)(B)(iii); 35 U.S.C. § 271(e)(2).

After a bench trial, the district court found the asserted claims from each of Vanda's patents invalid as obvious. App., *infra*, 17a-75a. On appeal, the Federal Circuit affirmed. *Id*. at 1a-16a.

First, the court concluded that claim 3 of the RE604 patent—which claims a method of entraining a Non-24 sufferer to a 24-hour sleep-wake cycle by administering 20mg of tasimelteon once daily before a target bedtime—was obvious. App., *infra*, 4a-9a. In so holding, the Federal Circuit relied on a combination of prior art that included the disclosure of Vanda's ongoing phase III clinical trial in Non-24, a summary of results of an earlier phase II clinical trial that had found a statistically significant effect only for 100mg of tasimelteon, and information about a different compound (melatonin). *Id.* at 4a-9a. The Federal Circuit credited the district court's finding that the prior art showed that "tasimelteon could * * * potentially

entrain patients suffering from circadian rhythm sleep disorders." *Id*. at 5a. Further, the court focused on a prior art reference suggesting that tasimelteon "may be useful in the treatment of sleep disturbances related to circadian rhythm sleep disorders." *Id.* at 6a. In evaluating the evidence, including a description of an "ongoing clinical trial," the Federal Circuit concluded that "the tasimelteon prior art would have given a skilled artisan a reasonable expectation of success of entrainment with 20mg." *Id*. at 8a.

Second, the court concluded that claim 5 of the '487 patent—which claimed a method of treating Non-24 by administering 20mg of tasimelteon "without food"—was obvious. App., *infra*, 9a-11a. The court relied on FDA guidance from 2002 advising that food can affect the bioavailability of drugs and generally recommending studying food's effect on drugs. *Ibid.* See also U.S. Food & Drug Admin., *Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies* (2002). Although the guidance makes clear that there are numerous possible permutations for food options—with food, without food, food agnostic, ignore certain foods, or within a certain time of meals (FDA, *supra*, at 2)—the court of appeals identified no other prior art that would have allowed a skilled artisan to predict tasimelteon's interaction with food. Rather, according to the court of appeals, it was enough that "food-effect studies were expected to be performed on new drugs" and "there were only two permutations for the food variable" to render the *result* of such an experiment obvious. App., *infra*, 9a-11a.

Third, the court held invalid as obvious Vanda's inventions that tasimelteon should not be taken with

another drug, rifampicin (a strong inducer of the enzyme CYP3A4, which reduces metabolism of the drug) or with a strong CYP1A2 inhibitor. App., *infra*, 11a-16a. The Federal Circuit found these method-of-treatment claims obvious based on literature about another compound (ramelteon). According to the court, because a skilled artisan "could not have ruled out an interaction between tasimelteon and a CYP3A4 inducer" or it would have been "reasonable to expect" that a CYP1A2 inhibitor would "negatively impact[] the efficacy of tasimelteon," the interaction patents were obvious. *Id*. at 14a, 16a.

In invalidating Vanda's patent claims, the Federal Circuit underscored the importance of its governing standard: "Obviousness does not require certainty—it requires a reasonable expectation of success." App., *infra*, 16a. The Federal Circuit thus affirmed the district court's judgment solely on the ground that all asserted claims were invalid for obviousness. *Ibid*.

REASONS FOR GRANTING THE PETITION

This Court's intervention is warranted to recalibrate the Federal Circuit's approach to the obviousness inquiry. The Federal Circuit holds that patent claims are obvious if the prior art merely provides a "reasonable expectation of success." That standard is materially lower than that long established by this Court and codified into Section 103; properly construed, prior art renders obvious those claimed inventions whose results were "predictable" at the outset. Indeed, prior to the creation of the Federal Circuit (and even once after), the regional circuits broadly embraced this correct standard for obviousness.

Setting the correct obviousness standard is an issue of utmost practical importance. That is especially true in the field of pharmaceutical innovation. Here, using its incorrect standard, the Federal Circuit found evidence that Vanda was undertaking clinical trials weighed in favor of obviousness. That conclusion—which stems from the Federal Circuit's incorrect obviousness standard—deeply unsettles innovation, as essentially all pharmaceutical advances depend on incremental work achieved via clinical trials.

A. The decision below conflicts with this Court's obviousness precedents and the animating purpose of Section 103.

Review is warranted because the Federal Circuit's reasonable-expectation-of-success standard—as well as its application of it—is inconsistent with the obviousness inquiry as construed by this Court. In fact, the Federal Circuit has clung to a test that is best understood as having been overturned by *KSR*.

The Court last addressed obviousness seventeen years ago, in *KSR*. The Court admonished the Federal Circuit for applying an obviousness test that was too "rigid" and incompatible with the statute and this Court's precedents. 550 U.S. at 415, 419. But the Federal Circuit has not retired its "rigid" obviousness standards. Rather, the Federal Circuit has continued to use its own reasonable-expectation-of-success standard and has applied it in a way that "limits the obviousness inquiry" by producing stark over-invalidation of patents not contemplated by the statute or this Court's precedents. *Id.* at 419.

1. The Federal Circuit's reasonable-expectation standard—an admitted "subsidiary requirement" imposed by the Federal Circuit (*Pfizer*, 480 F.3d at

1361)—conflicts with *KSR*. Rather than rigid rules, *KSR* taught that the "controlling inquiry" under Section 103, which has been in place since this Court first addressed Section 103 in *Graham*, is a straightforward one: "The scope and content of the prior art are * * * determined; differences between the prior art and the claims at issue are * * * ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *KSR*, 550 U.S. at 399 (quoting *Graham*, 383 U.S. at 17-18).

Both before and after *Graham*, this Court has employed a higher obviousness standard than what the Federal Circuit's reasonable-expectation standard has created. The Court has long protected "new and useful result[s]." *Winans* v. *Denmead*, 56 U.S. 330, 341 (1853). See also *Expanded Metal Co.* v. *Bradford*, 214 U.S. 366, 381 (1909) ("It is perfectly well settled that a new combination of elements, old in themselves, but which produce a new and useful result, entitles the inventor to the protection of a patent."). *KSR* thus explained that a "combination of familiar elements according to known methods is likely to be obvious *when it does no more than yield predictable results*." 550 U.S. at 416 (emphasis added). See also *id*. at 417 ("A court must ask whether the improvement is more than the *predictable* use of prior art elements according to their established functions." (emphasis added)).

KSR's holding reflects decades of consistent law: An invention is obvious only when it would have been "perfectly plain to an expert" (*Dow Chem.*, 324 U.S. at 327), or "immediately recognized" and "found ready at hand" by one skilled in the art (*De Forest Radio*, 283 U.S. at 682, 685), or "plainly indicated," or "plainly

foreshadowed" by the prior art (*Textile Mach. Works*, 302 U.S. at 497-498).

Rather than focusing on whether the end result was "predictable," the Federal Circuit's standard focuses on whether a "skilled artisan would have" "reasonab[ly] expect[ed]" to succeed in producing the result. App., *infra*, 5a-6a, 15a-16a; *Pfizer*, 480 F.3d at 1364 ("[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."). But a skilled artisan can reasonably *expect* success long before that success could be deemed "predictable." That is especially true in the chemical arts, where "[l]aboratory work of a decade is behind each discovery." *Chicago Steel Foundry Co.* v. *Burnside Steel Foundry Co.*, 132 F.2d 812, 817 (7th Cir. 1943). The very fact of designing an experiment in a pharmaceutical may give a reasonable expectation that the experiment would succeed; it would, after all, make little sense to conduct an experiment if it were expected to fail. Yet experimentation is often essential for invention.

The Court has distinguished hope or expectation that an experiment will succeed from circumstances where and when the success of that experiment is reduced to practice. For example, in *Eibel Process Co.* v. *Minnesota & Ontario Paper Co.*, the Court upheld a patent that used known components, each working according to known principles, because "there [was] no means, short of actual experiment, to enable one to anticipate results." 261 U.S. 45, 62 (1923). The result—raising one end of the machine to rely on gravity—had not been predictable, even if success might have been reasonably expected by knowing that

"water will run down hill." *Id.* at 52. Yet, because it was "impossible to apportion each factor [of the new design] its real influence" without actual experimentation, the invention was deemed non-obvious. *Id.* at 62.

By contrast, in *Sinclair & Carroll Co.* v. *Interchemical Corp.*, 325 U.S. 327 (1945), the Court held invalid a patent on fast-drying printer ink because the selection of the essential ingredient was "not the product of long and difficult experimentation" but by reading from a list and "selecting a known compound to meet known requirements." 325 U.S. at 331, 335 (1945).

The Federal Circuit's standard conflicts with the lessons of *Eibel* and *Sinclair* because it effectively treats any "viable" experiment as one that necessarily gives a skilled artisan a reason to expect a successful result from the experiment, making that result obvious and unpatentable. In *Bayer Schering Pharma AG* v. *Barr Laboratories, Inc*., for example, the Federal Circuit held invalid a patent on a micronized form of birth control because it found that micronization was a "viable option" and therefore a skilled artisan had a reasonable expectation of success. 575 F.3d 1341, 1348 (Fed. Cir. 2009). But merely concluding that an experiment is *viable* suggests "that the experiment may or may not succeed." *Id.* at 1351 (Newman, J., dissenting). Just because an experimental option is "viable" does not mean the results are predictable. In effect, this standard requires a skilled artisan to "conduct[] experiments that were expected to fail" for the result to be non-obvious. *Ibid.*

Similarly, in *Merck & Cie* v. *Gnosis S.P.A*., the Federal Circuit held invalid a patent on a method of

treatment using the folate L-5-MTHF to treat increased homocysteine. 808 F.3d 829, 833 (Fed. Cir. 2015). The court relied on the combination of two preexisting patents—one which suggested that "elevated levels of homocysteine are often associated with folate deficiencies" and another that "highlight[ed] L-5-MTHF as a 'natural metabolite' of folate." *Id.* at 833-834. But this second patent only stated that there was "an increasing interest for the application of this natural metabolite as at least one active compound in a therapeutic agent." *Id.* at 842 (Newman, J., dissenting). Nothing in the second patent linked the compound with treating elevated homocysteine levels—and even if it had, an "increasing interest" in testing a certain compound falls far short of being able to *predict* that compound's success.

The Federal Circuit's continued reliance on the reasonable-expectation-of-success standard disregards the lessons of *KSR* and has, in application, resulted in a materially lower threshold for obviousness than that found in this Court's precedents and reaffirmed in *KSR*. Without the TSM test the *KSR* Court rejected, the reasonable-expectation-of-success standard has operated to invalidate an ever-increasing number of patents in ways out of step with this Court's precedents. See Ryan T. Holte & Ted Sichelman, *Cycles of Obviousness*, 105 Iowa L. Rev 107 (2019) (finding a significant increase in obviousness findings in the Federal Circuit after *KSR*).

2. The Federal Circuit's reasonable-expectation-of-success standard also conflicts with Section 103 by effectively resuscitating the long-obsolete requirement that a patent reflect a "flash of creative

genius"—a requirement Congress expressly rejected when it enacted the Patent Act in 1952.

Before 1952, patentability had been described as requiring a "flash of creative genius." *Cuno Eng'g Corp.* v. *Automatic Devices Corp.*, 314 U.S. 84, 91 (1941). Through Section 103, Congress expressly rejected this requirement, directing that "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103 (1964). As this Court explained in *Graham*, "Congress intended by the last sentence of section 103 to abolish the test it believed this Court announced in the controversial phrase 'flash of creative genius,' used in *Cuno*." *Graham*, 383 U.S. at 15.[3] See also 2 Donald S. Chisum, *Chisum on Patents* § 5.02 (2023) (noting widespread agreement on this point). *Either* "long toil and experimentation" or "a flash of genius" can lead to patentable results. See 35 U.S.C. § 103, Revisor's Notes.

In practice, however, the Federal Circuit's standard effectively reimposes the "creative genius" requirement by undercutting patentability in industries that rely on long toil and experimentation to achieve results. In pharmaceutical innovation, the "manner" of invention "necessarily builds upon past discoveries and requires considerable experimentation through trial and error." Kristen C. Buteau, *Deuterated Drugs: Unexpectedly Nonobvious?*, 10 J. High Tech. L. 22, 23 (2009). See also *Chicago Steel*, 132 F.2d at 815-816 ("[I]n the field of science nearly all advance is made in

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[3] Although the *Graham* Court interpreted the "inventive genius" language as a mere "rhetorical embellishment" rather than a heightened standard of patentability, it nevertheless recognized Congress's intent to dispel any reliance on such a concept. 383 U.S. at 15 n.7.

laboratories where many experiments are made and discoveries result from the trial and error method."). The scientific process naturally creates a crowded field of prior art containing multiple building blocks for future scientific discoveries. Against this backdrop, a skilled artisan might reasonably expect an experiment to succeed, even when the results of those experiments are still unpredictable.

As the Federal Circuit has applied its reasonable-expectation-of-success standard, the practicalities of lengthy experimental procedures effectively negate the patentability of the *results* of those experiments. In drug development, innovators must perform experiments using human subjects, and Congress requires the lengthy experimentation necessary to develop and test new drugs to be undertaken in public view. See 42 U.S.C. § 282(i), (j); 42 C.F.R. §§ 11.8, 11.28. An innovator must submit clinical trial protocols to the FDA, which publishes the ongoing nature of the study on clinicaltrials.gov. See 42 U.S.C. § 282(j)(2)(A). And for good reason—publication of clinical trial protocols can "help patients find trials for which they might be eligible, enhance the design of clinical trials and prevent duplication of unsuccessful or unsafe trials, improve the evidence base that informs clinical care, increase the efficiency of drug and device development processes, improve clinical research practice, and build public trust in clinical research." *Clinical Trials Registration and Results Information Submission*, 81 Fed. Reg. 64,982, 65,124 (Sept. 21, 2016).

The Federal Circuit's reasonable-expectation-of-success standard sets up a situation in which the fact of the experiment itself will render a successful *result* obvious, regardless of whether a skilled artisan could

have "predict[ed]" that success. In the chemical arts, in particular, the Federal Circuit's reasonable-expectation standard effectively requires that skilled artisans would need to think an experiment would *fail* for the result to be nonobvious. In a world where drug development costs range from $1 billion to $3 billion,[4] clinical studies on drugs that have no "reasonable" expectation of success are simply not done, a principal point made by defendants' expert witness in arguing for the patents' invalidity. C.A. App. 19288 ("I mean, if someone is going to be spending the time and money to do a big Phase 3 trial, all that effort, as well as money, then that would say to me, and to a person of ordinary skill in the art that clearly there was a reasonable expectation that they are going to succeed."). By allowing the fact of an experiment to itself indicate obviousness, the Federal Circuit's reasonable-expectation standard cannot be squared with Congress's express instruction that "[p]atentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103.

The Federal Circuit's reasonable-expectation-of-success rule conflicts with this Court's precedent and has no basis in the statutory text. The Court's review is warranted.

B. No other circuit has adopted the Federal Circuit's reasonable-expectation rule.

The standard for obviousness has divided the circuits. Although the Federal Circuit has long and ubiquitously applied a reasonable-expectation-of-success

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[4] Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* 2 (Apr. 2021), perma.cc/CD8K-TWB9.

standard that traces to its CCPA lineage, no other circuit ever embraced this analysis. To the contrary, the regional circuits—principally prior to the creation of the Federal Circuit, but also even more recently—have instead applied this Court's more stringent standard, sounding in whether the prior art would yield "predictable results."

The **Seventh Circuit** in 2019 resolved an obviousness question implicated by a permissive counterclaim without employing the reasonable-expectation-of-success standard. See *ABS Global, Inc.* v. *Inguran, LLC*, 914 F.3d 1054, 1064-1069 (7th Cir. 2019).[5] Instead, the court recognized that *Graham* sets the obviousness standard (*id.* at 1066) and relied on *KSR*'s emphasis that it is "*predictable*" results that inform obviousness (*id.* at 1068 (emphasis added)). Per the Seventh Circuit, "*KSR* emphasizes that an invention may be obvious as a matter of law if it employs a 'predictable solution' to a known problem." *Ibid*.

The Seventh Circuit appears consistent with the approach taken uniformly by the regional circuits, which addressed hundreds of obviousness cases prior to the transfer of jurisdiction to the Federal Circuit in October 1982. So far as we are aware, no regional circuit ever adopted the reasonable-expectation-of-success standard—notwithstanding several decisions that postdate its invention by the CCPA.

The **Ninth Circuit**, for example, concluded that "application of known principles to a known problem

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[5] The Federal Circuit has exclusive jurisdiction over appeals where the action "aris[es] under" the Patent Act or "in which a party has asserted a *compulsory* counterclaim arising under" the Patent Act. 28 U.S.C. § 1295(a)(1) (emphasis added).

by the use of devices already known and understood to produce a *predictable result* does not amount to invention." *Pierce* v. *Ben-Ko-Matic, Inc.*, 310 F.2d 475, 477 (9th Cir. 1962) (emphasis added). The key to this test was not whether there was a "reasonable expectation" that the result would be achieved—but rather whether it was in fact "predictable" to a skilled artisan. See also *Penn Int'l Indus.* v. *Pennington Corp.*, 583 F.2d 1078, 1082 (9th Cir. 1978) ("Even minor changes from the prior art can produce a patentable invention so long as the result could not have been predicted beforehand by a person skilled in the art."); *Saf-Gard Prods., Inc.* v. *Serv. Parts, Inc.*, 532 F.2d 1266, 1272 (9th Cir. 1976) (similar); *Hayes Spray Gun Co.* v. *E.C. Brown Co.*, 291 F.2d 319, 321-322 (9th Cir. 1961) ("[T]he proportioning result could not be predicted by the application of scientific laws; it could be discovered and proved only by the painful process of trial and error.").

The **Third Circuit** evaluated the obviousness of a patent on a new oral antibiotic that "yielded the unexpected property of being almost 100% absorbable into the bloodstream." *Eli Lilly & Co.* v. *Premo Pharm. Lab'ys, Inc.*, 630 F.2d 120, 122 (3d Cir. 1980). The Third Circuit held that, "[i]f the new compound, although structurally obvious, exhibits uses or traits that, at the time of their discovery, *were not predictable* to chemists or other persons skilled in the prior art, such differences indicate that the new compound is nonobvious for purposes of [Section] 103." *Id.* at 130 (emphasis added). Notably, the Third Circuit did not consider whether there was a reasonable expectation of success in synthesizing the new compound—indeed, the circuit recognized that the process to create the

compound was "fairly simple." *Id.* at 130-131. Nevertheless, because the properties of the resulting compound were *not* predictable, the invention was nonobvious. Earlier, the Third Circuit similarly held that an "invention was not involved" when "known principles, [applied] to a known problem, by the use of devices already known and understood" produced "a *predictable* result." *Hazeltine Corp.* v. *General Motors Corp.*, 131 F.2d 34, 39-40 (3d Cir. 1942) (emphasis added).

The **Fifth Circuit** held that, in the case of the highly unpredictable chemical arts, it is only when an "inventor's work * * * [is] no more novel or non-obvious than the conducting of a biological or physiological testing program among catalogued compounds or an easily formulated series of homologues or analogues that *logically or predictably should disclose helpful uses*," that a patent should be held obvious. *Eli Lilly & Co.* v. *Generix Drug Sales, Inc*., 460 F.2d 1096, 1103 (5th Cir. 1972). This holding is right in line with this Court's decision in *Sinclair*, 325 U.S. 327, which held that selecting among known compounds with known properties to perform a predictable function is not patentable invention.

The **Second Circuit** similarly concluded that when a patent "merely substituted one material for another and the substituted material performed *in a readily predictable manner because of its well known properties*," the patent is invalid for obviousness. *Ling-Temco-Vought, Inc.* v. *Kollsman Instrument Corp*., 372 F.2d 263, 267 (2d Cir. 1967) (emphasis added). Like those employed by the other circuits, this test focuses on whether the results claimed in the patent were *predictable*, not whether a skilled artisan would reasonably expect success. *Ibid.* See also

Digitronics Corp. v. *New York Racing Ass'n, Inc.*, 553 F.2d 740, 745 (2d Cir. 1977) (holding patent obvious because the method employed "was just what could have been predicted when those means were applied to perform that function").

Further, as a broad matter, the regional circuits routinely applied the obviousness standard this Court set forth in *Graham*—none adopted the reasonable-expectation-of-success analysis created by the CCPA and later adopted by the Federal Circuit.[6] As the Fifth Circuit explained, the Supreme Court outlined the obviousness test in *Graham* and "emphasized that 'strict observance' of those requirements is necessary." *Cathodic Prot. Serv.* v. *American Smelting & Ref. Co.*, 594 F.2d 499, 506 (5th Cir. 1979). See also *Republic Indus., Inc.* v. *Schlage Lock Co.*, 592 F.2d 963, 972 (7th Cir. 1979) ("[U]ntil Congress shall otherwise legislate or the Supreme Court shall otherwise specifically hold, this court will continue to apply the *Graham* analysis as the exclusive means by which to measure nonobviousness under section 103."). Nearly every regional circuit agreed that "obviousness must always be considered a factual question within the param-

[6] So far as we are aware, the reasonable-expectation-of-success formulation appeared only once in the regional circuits. In *Commonwealth Engineering Co. of Ohio* v. *Watson*, the D.C. Circuit quoted a district court decision, which in turn quoted a Patent Office rejection observing that there was "no invention in applying an old process to another and analogous material where there is at least a reasonable expectation of success." 293 F.2d 157, 158 (D.C. Cir. 1961) (quoting *Commonwealth Eng'g*, 188 F. Supp. at 545, quoting in turn the Patent Office Board of Examiners).

eters of *Graham*." *Norfin, Inc.* v. *Int'l Bus. Machs. Corp.*, 625 F.2d 357, 365 (10th Cir. 1980).[7]

This divergence warrants review. The regional circuits "with broader jurisdiction" are meant to "provide an antidote to the risk that [the Federal Circuit] may develop an institutional bias," and "[a]n occasional conflict in decisions may be useful in identifying questions that merit this Court's attention." *Holmes Grp., Inc.* v. *Vornado Air Circulation Sys., Inc.*, 535 U.S. 826, 838-839 (2002) (Stevens, J., concurring). Further review is appropriate here.

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[7] See also, *e.g.*, *Colortronic Reinhard & Co.* v. *Plastic Controls, Inc.*, 668 F.2d 1, 4 (1st Cir. 1981) ("In reviewing a ruling of obviousness under section 103, we are guided by the Supreme Court's decision in *Graham*."); *Formal Fashions, Inc.* v. *Braiman Bows, Inc.*, 369 F.2d 536, 538 (2d Cir. 1966) ("To satisfy the ultimate legal test, we are to make the preliminary factual inquiries outlined in *Graham*."); *Rengo Co.* v. *Molins Mach. Co.*, 657 F.2d 535, 544 (3d Cir. 1981) ("*Graham* definitely states the minimum criteria for satisfaction of Section 103."); *Kabushiki Kaisha Audio-Technica* v. *Atlantis Sound, Inc.*, 629 F.2d 978, 980 (4th Cir. 1980) ("[*Graham*] explains the inquiry a court must undertake to decide whether a patent is obvious."); *Nickola* v. *Peterson*, 580 F.2d 898, 912 (6th Cir. 1978) ("The standards for determining obviousness under 35 U.S.C. § 103 were established by the Supreme Court in *Graham*."); *Woodstream Corp.* v. *Herter's, Inc.*, 446 F.2d 1143, 1149 (8th Cir. 1971) (noting "the Supreme Court enunciated the guidelines of inquiry into obviousness under § 103" in *Graham*); *Sarkisian* v. *Winn-Proof Corp.*, 686 F.2d 671, 674 (9th Cir. 1981) ("the obviousness or non-obviousness of an invention under § 103, though ultimately a question of law, cannot be determined without strict adherence to those factual inquiries" from *Graham*).

C. This is an attractive vehicle to address this exceptionally important question.

The standard for obviousness is a tremendously important issue implicated in virtually every patent case. Leading commentators call it the "most important (and most frequently litigated) of the standards of patentability." 2 Chisum, *supra*, § 5.02. Nowhere is that more true than in the context of pharmaceutical patents, where parties are vigorously contesting the validity of hundreds of patents protecting novel innovation.

1. To begin, there is no disputing the magnitude of this issue. Proper calibration of the obviousness standard is essential to innovation. The patent system is "a carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in technology, in return for an exclusive monopoly for a limited period of time." *Pfaff* v. *Wells Elecs., Inc.*, 525 U.S. 55, 63 (1998). Without this "inducement [] to bring forth new knowledge" (*Graham*, 383 U.S. at 8-9), innovation falters. This is particularly true with respect to the chemical arts, where "[l]aboratory work of a decade is behind each discovery." *Chicago Steel*, 132 F.2d at 817.

Developing innovative new pharmaceutical therapeutics requires enormous investments of money, can take decades, and is an inherently risk-filled process. Recent CBO estimates confirm that the average research-and-development cost for a new drug to go from the laboratory through FDA approval is roughly $1 billion to $3 billion. CBO, *supra*, at 2; Thomas Moore et al., *Cost of Clinical Trials For New Drug FDA Approval Are Fraction of Total Tab*, Johns Hopkins Bloomberg Sch. Pub. Health (Sept. 24, 2018),

perma.cc/3DPD-WEWG. See generally Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20, 20-33 (May 2016).

The drug-development process is also extraordinarily time-consuming. Drug innovators must undertake costly laboratory research, nonclinical testing, and large-scale clinical testing to bring a product to market. This full process can take a decade or more, and drug developers do not receive any financial return on their investment throughout this entire development period. See, *e.g.*, CBO, *supra*, at 14; Biotechnology Innovation Organization, *Clinical Development Success Rates and Contributing Factors 2011-2020* 23 (Feb. 2021), perma.cc/6CU6-VX9J.

Even with this massive financial burden and lengthy clinical trial period, there is no guarantee an innovator's investment in research and development will be recouped, given the low likelihood of FDA approval. See, *e.g.*, BIO, *supra*, at 3, 14; CBO, *supra*, at 2. Patent protection is therefore an essential incentive for drug development; indeed, "pharmaceutical companies are rarely willing to develop drugs without patent protection." Benjamin Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 Tex. L. Rev. 503, 505 (2009).

Left to stand, the Federal Circuit's standard threatens to foreclose broad swaths of patent rights, particularly in the chemical arts, where invention by definition is achieved through lengthy experimentation. A drug developer, for example, is required to disclose ongoing clinical trials on clinicaltrials.gov. See 42 U.S.C. § 282(i). Those disclosures are increasingly being invoked in district courts as grounds to

invalidate a patent covering the invention resulting from that trial on the theory that someone who knows an experiment is ongoing would "reasonabl[y] expect[]" that experiment to succeed.[8] The Federal Circuit's application of its reasonable-expectation-of-success standard thus "has the ironic effect of turning progress in the pharmaceutical sciences against itself." Roin, *supra*, at 506. In other words, it effectively nullifies patent protection for pharmaceutical inventions based on the very scientific advances that "allowed researchers to identify them as ones that are likely to be effective." *Ibid.*

This case is just one example of the Federal Circuit's trend of finding weak evidence sufficient to support a "reasonable expectation of success" with respect to pharmaceutical patents. As the Federal Circuit has employed its standard, a "reasonable expectation of success" requires much less, in practice, than the proof needed to show a result is obvious under this Court's precedents.

For example, in *Hoffmann-La Roche Inc.* v. *Apotex Inc.*, the Federal Circuit found that an unexpectedly successful dosing regimen for osteoporosis medication of 150mg per month was obvious, even though no prior

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[8] See, *e.g.*, *Salix Pharms., Ltd.* v. *Norwich Pharms., Inc.*, 2022 WL 3225381, at *13-19 (D. Del. Aug. 10, 2022), *appeal filed*, Nos. 22-2153, 23-1952 (Fed. Cir. 2023) (release of phase II clinical trial protocol contributed to a reasonable expectation of success); *Bausch Health Ireland Ltd.* v. *Padagis Israel Pharms. Ltd.*, 2022 WL 17352334, at *31-32 (D.N.J. Dec. 1, 2022) (clinical trial evidence introduced to argue obviousness); *Janssen Pharms., Inc.* v. *Mylan Laby's Ltd.*, 2023 WL 3605733, at *18, 20 & n.17 (D.N.J. May 23, 2023) (same), *appeal filed*, No. 23-2042 (Fed. Cir. June 20, 2023); *Sanofi-Aventis U.S. LLC* v. *Sandoz, Inc.*, 2023 WL 4175334, at *14 (D. Del. June 26, 2023) (same).

art studied either a 150mg dose or monthly administration. 748 F.3d 1326 (Fed. Cir. 2014). Nevertheless, the Federal Circuit deemed this solution obvious because 150mg per month is equivalent to a 5mg daily dose that had been studied, ignoring the fact that the prior art deemed 2.5mg the "most effective dose." *Id*. at 1338 (Newman, J., dissenting).

In *Sanofi-Aventis Deutschland GMBH* v. *Mylan Pharmaceuticals Inc.*, 791 F. App'x 916 (Fed. Cir. 2019), and *Scientific Plastic Products, Inc.* v. *Biotage AB*, 766 F.3d 1355 (Fed. Cir. 2014), the Federal Circuit relied on the patents' own specifications as evidence of obviousness, even when those specifications revealed information not disclosed elsewhere in the prior art. Finally, the District of Delaware, employing the Federal Circuit's reasonable-expectation-of-success standard, relied in part on the disclosure of a clinical trial protocol to find a drug breakthrough obvious. *Salix Pharms.,* 2022 WL 3225381, at *19.

The Federal Circuit's standard for obviousness thus erodes the incentives for invention that the patent system was designed to protect, which will in turn reduce the number of breakthrough treatments available to the public.

The importance of this Court's consideration of this issue is all the more critical in light of its decision last term in *Amgen Inc.* v. *Sanofi*, 598 U.S. 594 (2023). There, the Court reiterated that a drug innovator cannot patent its novel methods without possessing sufficient detail to explain to another the scope of the invention, which often requires the *results* of clinical trials. *Id.* at 613-615. By allowing the existence of an ongoing study or FDA suggestions of possible studies as indicia of obviousness, the Federal Circuit's decision

below all but forecloses a drug manufacturer's attempt to reach the very results *Amgen* requires for patentability under Section 112.

That is, under *Amgen*, it is generally too early to patent pharmaceutical method claims prior to obtaining the results of clinical trials. But, under the Federal Circuit's wayward approach to obviousness, once clinical trials are announced, it is *too late* to patent eventual discoveries, *because* the announcement of the trial itself will render obvious the resulting invention. The Federal Circuit's standard should be reviewed—and corrected.

2. This case is an attractive vehicle for resolving these important issues. Obviousness was the sole basis for the decision below. App., *infra*, 1a-16a. And the Federal Circuit's application of its reasonable-expectation-of-success standard resulted in that conclusion: For Vanda's method of treating Non-24 with 20mg of tasimelteon (the RE604 patent), the court of appeals upheld the conclusion that the prior art "would have given a skilled artisan a reasonable expectation of success of entrainment with 20 mg" (App., *infra*, 8a), and for Vanda's drug-drug interaction patents, an inability "to rule out" an interaction or to "reasonably expect[]" an interaction resulted in an obviousness finding (*id.* at 14a-16a).

Had the Federal Circuit properly adhered to the standards in *Graham* and *KSR* and focused on whether the prior art made it *predictable* that Vanda's patented inventions would be achieved, rather than whether the prior art made it reasonable to expect them to result, it would have reversed.

First, the panel held that Vanda's patented method of administering 20mg of tasimelteon to

entrain a Non-24 patient's circadian rhythm was obvious based on an article suggesting that melatonin could entrain Non-24 patients, a small trial that showed 100mg of a tasimelteon (but not 20mg) produced a statistically significant phase shift in a study of patients with insomnia (not Non-24), and the existence of Vanda's ongoing clinical trial for tasimelteon to treat Non-24. App., *infra*, 5a-8a.

Although Vanda was conducting a phase III clinical trial, it did not yet have the *results* of that clinical trial, which demonstrated that 20mg of tasimelteon can indeed entrain a Non-24 sufferer's circadian rhythm, and it was that invention Vanda patented. From these datapoints, a skilled artisan certainly could not have *predicted* that Vanda's clinical trial would succeed in showing that 20mg of tasimelteon could entrain a Non-24 sufferer's circadian rhythm, even though one might have "reasonably expected" that the clinical trial would succeed by the very fact that Vanda was performing it. Cf. C.A. App. 19288 (defendants' expert testifying that "spending the time and money to do a big Phase 3 trial * * * would say to me, and to a person of ordinary skill in the art, that clearly there was a reasonable expectation that they are going to succeed."). It is the difference between thinking Vanda's clinical trial *could* work versus being able to predict that it *would* work in achieving this "new and beneficial result" (*Webster Loom*, 105 U.S. at 591). See also *Diamond Rubber Co. of New York* v. *Consol. Rubber Tire Co.*, 220 U.S. 428, 443 (1911) (when "success could only have been achieved by careful study," the result is non-obvious).

Second, with respect to Vanda's drug-drug interaction patents, the prior art referenced a drug-drug

interaction between a different compound (ramelteon) and rifampicin, a CYP3A4 inducer. Although the panel recognized that the prior art did not report an interaction between rifampicin and tasimelteon, the panel nonetheless concluded that it was possible there could be such an interaction and that a skilled artisan "could not have ruled out" the possibility of an interaction based on what was known about ramelteon. App., *infra*, 12a-14a.

While that conclusion may satisfy the Federal Circuit's standard that a skilled artisan need only be able to "reasonably expect" a result, it cannot be squared with *KSR*'s predictability principle. That a skilled artisan "could not have ruled [an interaction] out" and might therefore be cautious enough not to coadminister tasimelteon with rifampicin cannot possibly mean that the interaction is a "predictable result" (*KSR*, 550 U.S. at 416) based on what was known.

Similarly, for Vanda's invention that tasimelteon should not be coadministered with CYP1A2 inhibitors, the panel observed that the prior art indicated that one should exercise "caution" before coadministering tasimelteon and a CYP1A2 inhibitor. That word of caution, the court of appeals held, meant that a skilled artisan would have a "reasonable expectation of success" in achieving Vanda's invention. But that does not mean it is *predictable* that tasimelteon *would* interact with a CYP1A2 inhibitor—which is what Vanda's experimentation showed and its patent claimed. Instead, the Federal Circuit precludes patentability only because something "could" theoretically work. That materially heightens the patentability standard above what this Court's precedents support. See *Graham*, 383 U.S. at 36 (patent's claims

were obvious because they were "clearly evident from the prior art").

Third, the panel invalidated Vanda's food-effects patent based solely on the FDA's suggestion in guidance that food effects should be studied because it is generally known that food can change a drug's bioavailability. App., *infra*, 9a-11a. In other words, it was enough that "food-effect studies were expected to be performed on new drugs" and "there were only two permutations for the food variable" for the *result* of such an experiment to be obvious. This holding misunderstands *KSR*'s obvious-to-try analysis. A solution is "obvious to try" only when there is a "known problem" and a person of ordinary skill has "a finite number of identified, predictable solutions * * * within his or her technical grasp." *KSR*, 550 U.S. at 420, 421. But nothing in the prior art suggested that the patented method was one of a finite number of "predictable solutions." Quite the contrary. The options available—to administer tasimelteon with food, without food, avoid certain foods, or food agnostic—are not equally viable predictable solutions. Only one—taking tasimelteon without food—is a successful method of administering tasimelteon. And this result was not predicted by the prior art: as of the priority date, no public knowledge about any potential food interaction with tasimelteon existed.

Thus, while the general idea that food may affect a drug's bioavailability was well known, the specific effect of food on tasimelteon was not known until tested. This Court has previously held that, when the outcome of an inventive process was not predictable, but only obtained as the result of "actual experiment[ation]," the invention is patentable. *Eibel*, 261

U.S. at 62. That is exactly the case here. The evidence established that for tasimelteon to be effective, a "short pulse" of the drug is required to reset the circadian clock. C.A. App. 19031. There was nothing in the prior art that predicted whether and how ingestion of food might affect the bioavailability of the drug during this "short pulse." Vanda's invention—directing that tasimelteon should be taken without food—required more than merely "implement[ing] a predictable variation" of the prior art. *KSR*, 550 U.S. at 417. Had the Federal Circuit applied the correct predictability standard, it would not have held Vanda's food effect patent obvious.

* * *

This Court has consistently held over many decades that patent claims are invalid as obvious only where the result would have been "perfectly plain" (*Dow Chem.*, 324 U.S. at 327), "immediately recogniz[able]" and "found ready at hand" (*De Forest Radio*, 283 U.S. at 682, 685), "plainly indicated" or "plainly foreshadowed" (*Textile Mach.*, 302 U.S. at 497, 498), or "predictable" to one skilled in the art (*KSR*, 550 U.S. at 416). The regional circuits had long applied this law. But the Federal Circuit continues to adhere to its own "subsidiary requirement" (*Pfizer*, 480 F.3d at 1361) that obviousness turns on whether a skilled artisan would have had a "reasonable expectation of success" in achieving the patented result.

As this case illustrates, the difference in these standards is quite material—here, it led to the wrong result. And the Federal Circuit's incorrect standard has broad implications beyond this case. Continued application of the reasonable-expectation-of-success test will mean the existence of a clinical trial or

federal guidance generally recommending certain experiments will render the results of those experiments obvious, no matter how innovative or unpredictable. This, in turn, threatens to erode the balance of incentives that the patent system was designed to protect, especially in the chemical arts, where "long toil and experimentation" is essential to achieving innovation.

CONCLUSION

The Court should grant the petition.

Respectfully submitted.

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