No. 11-879

IN THE

Supreme Court of the United States

APOTEX INC. AND APOTEX CORP.,

Petitioners,

v.

UNIGENE LABORATORIES, INC., AND UPSHER-SMITH LABORATORIES, INC.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

REPLY BRIEF FOR PETITIONERS

ROBERT S. SILVER
MANNY D. POKOTILOW
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street
11th Floor
Philadelphia, PA 19103
(215) 567-2010

ROY T. ENGLERT, JR.
Counsel of Record
ALAN E. UNTEREINER
DANIEL N. LERMAN
Robbins, Russell, Englert, Orseck, Untereiner & Sauber LLP
1801 K Street, N.W.
Washington, D.C. 20006
(202) 775-4500
renglert@robbinsrussell.com

Counsel for Petitioners

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The "lead compound" test applied by the Federal Circuit in this case (and in all chemical-compound cases) conflicts with the "obvious to try" test endorsed in *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398, 421 (2007). The proper inquiry under the "obvious to try" test is whether a person having ordinary skill in the art ("PHOSITA") would have been motivated to experiment with known elements. If so, then the outcome of that experimentation would have been obvious. Applying the "lead compound" test, however, the court below instead asked whether it would have been obvious to arrive at a *specific result*—the use of a particular concentration of a particular inactive ingredient. The "lead compound" test effectively renders the "obvious to *try*" test a nullity.

Respondents contend that this case would not be a suitable vehicle to address the "lead compound" test, but every argument they make illustrates why this case would be an ideal vehicle to address the question presented. For example, the lower court acknowledged—and respondents concede (at 12)—that a PHOSITA would have been motivated to create a "bioequivalent" copy of Miacalcin®. The fact that the court nevertheless upheld the validity of the copycat formulation perfectly illustrates how the Federal Circuit's erroneous standard undermines the "obvious to try" test articulated by this Court.

Respondents also argue that Apotex should not be permitted to challenge the "lead compound" test because it did not directly challenge that test below. But Apotex plainly argued below that the patent-in-

suit is invalid as obvious. Once such a federal claim is presented, a party is not limited to the precise arguments that it made below. The validity of the "lead compound" test is squarely before this Court.

I. THE "LEAD COMPOUND" TEST CONFLICTS WITH *KSR* AND RENDERS THE "OBVIOUS TO TRY" TEST A NULLITY

In *KSR*, this Court recognized that, even without a specific teaching, suggestion, or motivation in the prior art to combine known elements, a particular combination of known elements could be "obvious to try." *KSR*, 550 U.S. at 421. Under the "lead compound" test, however, a challenger must show a teaching, suggestion, or motivation *both* to select a lead compound *and* to modify it in a particular way. *Takeda Chem. Indus., Ltd.* v. *Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007). The rigid "lead compound" test is therefore directly at odds with the "obvious to try" test. If "obvious to try" were not the test, this Court would not have confirmed in *KSR* that the "combination of familiar elements according to known methods is likely to be obvious, when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

Respondents counter that the "'obvious to try' theory is simply inapposite in the present case." Opp. 19. In support, they state that the Federal Circuit acknowledged the "obvious to try" test, but "determined that 'about 20mM citric acid' was *not* a predictable solution to the problem facing" a PHOSITA. *Ibid.* But that conclusion only underscores how the Federal Circuit's "lead

compound" test renders the "obvious to try" test a dead letter.

The Federal Circuit recognized—and respondents do not dispute—that "design need and market demand" would have motivated a PHOSITA to create a "bioequivalent" copy of Miacalcin®. Pet. App. 18a-19a. Applying the "lead compound" test, however, the Federal Circuit then asked the wrong question. It asked whether the specific result—the use of "20mM citric acid"—was a predictable solution to the problem of creating a bioequivalent to Miacalcin®. But the "obvious to try" test does not require a motivation to arrive at a particular *result*. Rather, the "obvious to try" test asks whether it would be obvious to *experiment* with the "known options within [a PHOSITA's] technical grasp." *KSR*, 550 U.S. at 421.

Here, the prior art taught a "finite number" of possible absorption enhancers that can be used to increase the bioavailability of calcitonin, the active ingredient in Miacalcin®. *KSR*, 550 U.S. at 421; cf. *Takeda*, 492 F.3d at 1357 (prior-art patent disclosed "hundreds of millions" of potential lead compounds). Under this Court's "obvious to try" test, the Federal Circuit should have asked whether it would have been obvious to *experiment* with those absorption enhancers—including but not limited to citric acid—in order to try to create a composition that was bioequivalent to Miacalcin®. Instead, the Federal Circuit asked whether it would have been obvious to select a particular absorption enhancer (citric acid) in a particular concentration (20 mM) to arrive at a particular result. That is a nearly impossible

standard to satisfy, and conflicts with the "obvious to try" test endorsed by this Court.

Respondents suggest that, because "[t]here is no dispute that Miacalcin® is the appropriate starting place for the obviousness analysis," the Federal Circuit properly applied the "lead compound" test in this case. Opp. 24. But the "lead compound" test has *two* mandatory steps: that a PHOSITA would have been motivated to select a lead compound as a starting point; and that "the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda*, 492 F.3d at 1356 (internal quotation marks omitted).

By applying the rigid two-step "lead compound" test, the Federal Circuit relegated Miacalcin® to the first step of the inquiry. But the fact that a person of skill in the art was motivated to copy Miacalcin® is relevant—and indeed case-dispositive—to the obviousness analysis as a whole. For example, respondents repeatedly state (at 16, 18, 19) that the prior art did not specifically disclose the particular concentration of citric acid claimed in claim 19. That assertion misses the point. Because market forces created a motivation to develop a bioequivalent to Miacalcin®, it would have been "obvious to try" various concentrations of citric acid to see which concentration ensured that Fortical® delivers the same amount of calcitonin as does Miacalcin®; 20 mM just *happened to be* the concentration that did so.

Although respondents argue (at 25-26) that the "lead compound" test is necessary to "guard against improper hindsight," this Court rejected that same

argument in *KSR*. There, the Federal Circuit had determined that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *Teleflex, Inc.* v. *KSR Int'l Co.*, 119 F. App'x 282, 285 (Fed. Cir. 2005) (internal quotation marks omitted). This Court concluded that the Federal Circuit "drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias." *KSR,* 550 U.S. at 421. "Rigid preventative rules that deny factfinders recourse to common sense," the Court explained, "are neither necessary under our case law nor consistent with it." *Ibid.* The "lead compound" test is precisely such a "[r]igid preventative rule[]," and cannot be rehabilitated by saying it combats hindsight bias.[1]

Finally, respondents contend that "the 'lead compound' framework is not mandatory," Opp. 22, 26, and therefore does not violate this Court's directive not to use "rigid" or "mandatory formulas" to determine obviousness, *KSR*, 550 U.S. at 419. But that assertion conflicts with the Federal Circuit's own characterization of the "lead compound" test, which demonstrates that the test is mandatory in chemical-compound cases. See, *e.g.*, *Takeda*, 492

[1] The "obvious to try" test that the Federal Circuit should have applied in this case properly guards against hindsight bias because it asks whether "design need or market pressure" at the time of the invention would have given a PHOSITA "reason to pursue the known options within his or her technical grasp." *KSR*, 550 U.S. at 421. It just does so without also imposing a rigid and mandatory rule that artificially limits the obviousness inquiry.

F.3d at 1357 ("in cases involving new chemical compounds, it remains *necessary* to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness") (emphasis added); *Altana Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009) ("the accused infringer *must* identify some reason that would have led a chemist to modify a known compound in a particular manner") (emphasis added); *Eli Lilly & Co.* v. *Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2007) (describing "require[d]" showing under lead compound test). Those cases show that the Federal Circuit treats the "lead compound" test as obligatory.[2] They also show that the Federal Circuit applies a different test for compounds than the test this Court set forth in *KSR* and prior cases.

II. THIS CASE IS AN IDEAL VEHICLE FOR RESOLVING THE QUESTION PRESENTED

Respondents do not deny the importance of the question presented. That is not surprising, given the critical importance of pharmaceutical compositions for human health—and the need to ensure that the patent monopoly is not granted to marginal advances in the field. See Pet. 23-27. Nor do respondents dispute the "bare fact," Opp. 10, that, applying the "lead compound" test, the Federal Circuit had found nonobviousness in *every* chemical compound case

[2] It bears repeating that, if Congress wanted to establish a special obviousness test for chemical-compound cases, it would have done so. See 35 U.S.C. § 103(b) (obviousness rule for "biotechnological process[es]"). Respondents have no answer to this point.

since *KSR*—proof that the "lead compound" test creates a nearly insurmountable hurdle for obviousness-based challenges in chemical cases.

Respondents instead contend that this case presents a poor vehicle for this Court to address the "lead compound" test. First, they assert that "this is a formulation case, not a compound case." Opp. 12. But that just shows how far the Federal Circuit is willing to extend the "lead compound" test: from new chemical compounds to *all* pharmaceutical formulations. That mission creep is a reason to grant certiorari, not to deny it. Furthermore, Congress created the ANDA and "paper NDA" approval mechanisms to encourage the development of low-cost generic drugs. That important policy objective is thwarted by the application of the "lead compound" test to protect copycat pharmaceutical formulations.

Second, respondents state that no other case has considered the obviousness of a formulation specifically designed to be "bioequivalent to a prior art formulation." Opp. 12. But that fact also weighs strongly in favor of certiorari. It is undisputed that the patented composition here is an intentional copy of another commercially successful nasal spray containing the same active ingredient in the same active concentration. The only difference between the original (Miacalcin®) and the copy (Fortical®) is that Fortical® uses inactive ingredients that were known to provide the same functions as those used in Miacalcin®. The Federal Circuit's holding that those minor substitutions nevertheless would not have been obvious illustrates how the procrustean two-

step "lead compound" test vitiates the "obvious to try" test from *KSR*.

Third, respondents note that the USPTO reissued claim 19 after considering Apotex's prior-art references. Opp. 13. As we explained (Pet. 26), however, the USPTO has expressly adopted the Federal Circuit's "lead compound" framework. It is therefore not surprising that the USPTO initially reached the same flawed conclusion as the Federal Circuit. Indeed, the USPTO's application of the rigid "lead compound" test underlines that the test has profound consequences for the thousands of pharmaceutical patents issued each year—not just those that wind up in litigation. This is an issue of critical importance.

Finally, respondents allude to "complicating factual issues" and contend that Apotex is really complaining about factual "theories" it lost below. Opp. 12-13. But "[t]he ultimate judgment of obviousness is a legal determination," *KSR*, 550 U.S. at 427. On summary judgment, the district court concluded (and the Federal Circuit affirmed) that Apotex "failed to meet [its] burden of proving obviousness *as a matter of law*." Pet. App. 75a (emphasis added); see *id.* at 23a.

The fact that the courts below reached that legal conclusion by applying the "lead compound" test underscores the dispositive effect of the Federal Circuit's flawed legal standard—and the suitability of this case as a vehicle for resolving the purely legal question presented. If this Court holds that the "lead compound" test is inconsistent with its precedents, any outstanding factual disputes can be resolved on remand.

III. APOTEX'S CHALLENGE TO THE VALIDITY OF THE "LEAD COMPOUND" TEST IS PROPERLY BEFORE THIS COURT

Respondents argue that Apotex "did not challenge the 'lead compound' framework" below. Opp. 9. They say Apotex "embraced" the lead-compound test and therefore "should not be permitted to challenge it for the first time before this Court." *Id.* at 10.

This Court, however, has stated that, "'[o]nce a federal claim is properly presented, a party can make any argument in support of that claim; parties are not limited to the precise arguments they made below.'" *Lebron* v. *Nat'l R.R. Passenger Corp.*, 513 U.S. 374, 379 (1995) (quoting *Yee* v. *Escondido*, 503 U.S. 519, 534 (1992)). Respondents acknowledge that Apotex argued in both the district court and in the court of appeals that claim 19 would have been obvious in light of the prior art. Opp. 5, 7. Apotex squarely presented the "federal claim" at issue here: obviousness. See 35 U.S.C. § 103(a). It can therefore "make any argument in support of that claim," *Lebron*, 513 U.S. at 379 (internal quotation marks omitted).

"[E]ven if this *were* a claim not raised by petitioner below," moreover, this Court "would ordinarily feel free to address it, since it was addressed by the court below." *Lebron*, 513 U.S. at 379. This Court's practice "'permit[s] review of an issue not pressed so long as it has been passed upon.'" *Ibid.* (quoting *United States* v. *Williams*, 504 U.S. 36, 41 (1992)). Both the district court and the Federal Circuit expressly relied on the "lead compound" test to reject Apotex's obviousness

challenge. The question whether that rigid test is consistent with *KSR* is therefore properly before this Court.

Indeed, by respondents' logic, the question this Court resolved in *KSR* itself was not properly raised. In *KSR*, the petitioner argued in the Federal Circuit that the district court had correctly applied the TSM test to invalidate the patent-in-suit. See *Teleflex,* 119 F. App'x at 286. After the Federal Circuit reversed, the petitioner sought review in this Court on the ground that the TSM test applied by the lower courts had "no basis in the text of § 103 or in any decision of this Court." Pet. for Writ of Certiorari at 4, *KSR*, 550 U.S. 398 (2007) (No. 04-1350), 2005 WL 835463. This Court granted certiorari to address the same test the petitioner had "embraced" in both the district court and the court of appeals.

And for good reason. The rigid TSM test was at the time the law in the circuit—a circuit with exclusive jurisdiction over patent appeals. The petitioner in *KSR* therefore had no choice but to accept the established (but erroneous) framework set by precedents of the circuit in which it was litigating. So too here. As discussed above, the Federal Circuit has proclaimed the "lead compound" test the exclusive test for determining obviousness in chemical-compound cases. It would have been futile to argue below that the Federal Circuit's binding precedent was simply wrong.

In any event, respondents' repeated assertion (at 5, 7, 10) that Apotex "embraced" the lead-compound test below is baseless. Apotex did not even *mention* the "lead compound" test in its briefing below—much less "embrace" it. Instead, Apotex argued that the

"common sense" approach adopted by this Court in *KSR* is the correct approach and that the district court failed to properly apply that test. Br. for Defs. at 33, *Unigene Labs., Inc.* v. *Apotex, Inc.*, No. 2010-1006 (Fed. Cir. Oct. 18, 2010), 2010 WL 4600066; *id.* at 17-18 (arguing that, "'when a patent "simply arranges old elements with each performing the same function it had been known to perform" and yields no more than one would expect from such an arrangement, the combination is obvious'") (quoting *KSR*, 550 U.S. at 417). That is precisely the argument Apotex presses here.

Respondents' other efforts to avoid this Court's review also miss the mark. Respondents argue that "Apotex did not even seek *en banc* review from the Federal Circuit." Opp. 10. True enough, but this Court has never required petitioners to seek rehearing *en banc* before filing a petition for certiorari—a fact again illustrated by *KSR*, in which the petitioner chose not to seek rehearing in the Federal Circuit before petitioning (successfully) for certiorari. Pet. for Writ of Certiorari at 1, 2005 WL 835463. Moreover, the Federal Circuit has denied rehearing *en banc* in other cases implicating the validity of the "lead compound" test. *E.g.*, *Eli Lilly & Co.* v. *Zenith Goldline Pharms., Inc.*, 471 F.3d 1369 (Fed. Cir. 2007).

Finally, respondents attempt to muddy the waters by suggesting that Apotex failed "to raise the '014 patent on summary judgment in the district

court." Opp. 13 & n.15, 17, 18.[3] As Apotex argued when respondents pressed that same argument in the Federal Circuit, however, Apotex cited the '014 patent numerous times in the summary-judgment proceedings and in other proceedings in the district court. Reply Br. for Defs. at 10-11, *Unigene Labs.*, No. 2010-1006 (Fed. Cir. Dec. 20, 2010), 2010 WL 5558492. The Federal Circuit clearly agreed, as its obviousness analysis centered on that prior-art patent. Pet. App. 20a. Respondents cannot avoid this Court's review by resurrecting a meritless forfeiture argument that was disregarded by the court below. See *Lebron*, 513 U.S. at 379 (permitting review of issues "passed upon" by the court of appeals) (internal quotation marks omitted).

[3] The '014 patent lists as inventor Dr. Stern, the same inventor listed on the patent at issue in this case. It teaches that citric acid enhances the bioavailability of salmon calcitonin—a fact that would therefore have been well known to a PHOSITA at the time of the "invention" at issue here. See Pet. 7, 28.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

ROBERT S. SILVER
MANNY D. POKOTILOW
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street
11th Floor
Philadelphia, PA 19103
(215) 567-2010

ROY T. ENGLERT, JR.
Counsel of Record
ALAN E. UNTEREINER
DANIEL N. LERMAN
Robbins, Russell, Englert, Orseck, Untereiner & Sauber LLP
1801 K Street, N.W.
Washington, D.C. 20006
(202) 775-4500
renglert@robbinsrussell.com

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